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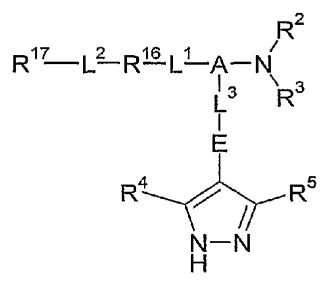
(54) Title: PHARMACEUTICAL COMPOUNDS



(I)

(57) **Abstract:** The invention provides a compound of the formula (I) or a salt, solvate, tautomer or N-oxide thereof; wherein A is a saturated hydrocarbon linker group; E is a monocyclic or bicyclic carbocyclic or heterocyclic group; L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONR', -NR'CO, -S, -C(O)-, -C(NR^{11})-, -C(S)-, -N(R^{11})$_2$, C(=CHR^{11}), -SO- and -SO$_2$-; or L^1 together with t R^{16} forms and 8-12 membered fused bicyclic heteroaryl ring system; L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously; R^{16} is an optionally substituted 5- to 12-membered monocyclic or bicyclic carbocyclic or heterocyclic ring; L^2 is absent or is a linker selected from C]-C4 alkylene, Ci-C4 alkenylene, Ci-C4 alkynylene, -CONR'-, -NR'CO-, -O-, -S-, -C(O)-, C(=CHR^{11}), C(S)-, -N(R^{11})$_2$, C_{3-4} cycloalkanediyl, -SO- and -SO2-; R^{17} is absent or is C_{1-6} alkyl or an optionally substituted 5 to 12 membered carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent; and R^2, R^3, R^4, R^5, R^{11} and R' are as defined in the claims.

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PHARMACEUTICAL COMPOUNDS

This invention relates to pyrazole-containing aryl- and heteroaryl-alkylamine compounds that inhibit or modulate the activity of protein kinase B (PKB) and protein kinase A (PKA), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by PKB and PKA, and to novel compounds having PKB and PKA inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II,* Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.,* 9:576-596 (1995); Knighton, *et al., Science,* 253:407-414 (1991); Hiles, *et al., Cell,* 70:419-429 (1992); Kunz, *et al., Cell,* 73:585-596 (1993); Garcia-Bustos, *et al., EMBO J.,* 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein

phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, diseases and conditions of the immune system, diseases and conditions of the central nervous system, and angiogenesis.

Apoptosis or programmed cell death is an important physiological process which removes cells no longer required by an organism. The process is important in early embryonic growth and development allowing the non-necrotic controlled breakdown, removal and recovery of cellular components. The removal of cells by apoptosis is also important in the maintenance of chromosomal and genomic integrity of growing cell populations. There are several known checkpoints in the cell growth cycle at which DNA damage and genomic integrity are carefully monitored. The response to the detection of anomalies at such checkpoints is to arrest the growth of such cells and initiate repair processes. If the damage or anomalies cannot be repaired then apoptosis is initiated by the damaged cell in order to prevent the propagation of faults and errors. Cancerous cells consistently contain numerous mutations, errors or rearrangements in their chromosomal DNA. It is widely believed that this occurs in part because the majority of tumours have a defect in one or more of the processes responsible for initiation of the apoptotic process. Normal control mechanisms cannot kill the cancerous cells and the chromosomal or DNA coding errors continue to be propagated. As a consequence restoring these pro-apoptotic signals or suppressing unregulated survival signals is an attractive means of treating cancer.

The signal transduction pathway containing the enzymes phosphatidylinositol 3-kinase (PI3K), PDK1 and PKB amongst others, has long been known to mediate increased resistance to apoptosis or survival responses in many cells. There is a substantial amount of data to indicate that this pathway is an important survival pathway used by many growth factors to suppress apoptosis. The enzyme PI3K is activated by a range of growth and survival factors e.g. EGF, PDGF and through the generation of polyphosphatidylinositols, initiates the activation of the downstream signalling events including the activity of the kinases PDK1 and protein kinase B (PKB) also known as Akt. This is also true in host tissues, e.g. vascular endothelial cells as well as neoplasias. PKB is a protein ser/thr kinase consisting of a kinase domain together with an N-terminal PH domain and C-terminal regulatory domain. The enzyme PKB itself is phosphorylated on Thr 308 by PDK1 and on Ser 473 by an as yet unidentified kinase. Full activation requires phosphorylation at both sites whilst association between PIP3 and the PH domain is required for anchoring of the

enzyme to the cytoplasmic face of the lipid membrane providing optimal access to substrates.

Activated PKB in turn phosphorylates a range of substrates contributing to the overall survival response. Whilst we cannot be certain that we understand all of the factors responsible for mediating the PKB dependent survival response, some important actions are believed to be phosphorylation and inactivation of the pro-apoptotic factor BAD and caspase 9, phosphorylation of Forkhead transcription factors e.g. FKHR leading to their exclusion from the nucleus, and activation of the NfkappaB pathway by phosphorylation of upstream kinases in the cascade.

In addition to the anti-apoptotic and pro-survival actions of the PKB pathway, the enzyme also plays an important role in promoting cell proliferation. This action is again likely to be mediated via several actions, some of which are thought to be phosphorylation and inactivation of the cyclin dependent kinase inhibitor of $p21^{Cip1/WAF1}$, and phosphorylation and activation of mTOR, a kinase controlling several aspects of cell growth.

The phosphatase PTEN which dephosphorylates and inactivates polyphosphatidyl-inositols is a key tumour suppressor protein which normally acts to regulate the PI3K/PKB survival pathway. The significance of the PI3K/PKB pathway in tumourigenesis can be judged from the observation that PTEN is one of the most common targets of mutation in human tumours, with mutations in this phosphatase having been found in ~50% or more of melanomas (Guldberg et al 1997, Cancer Research 57, 3660-3663) and advanced prostate cancers (Cairns et al 1997 Cancer Research 57, 4997). These observations and others suggest that a wide range of tumour types are dependent on the enhanced PKB activity for growth and survival and would respond therapeutically to appropriate inhibitors of PKB.

There are 3 closely related isoforms of PKB called alpha, beta and gamma, which genetic studies suggest have distinct but overlapping functions. Evidence suggests that they can all independently play a role in cancer. For example PKB beta has been found to be over-expressed or activated in 10 – 40% of ovarian and pancreatic cancers (Bellacosa et al 1995, Int. J. Cancer 64, 280 – 285; Cheng et al 1996, PNAS 93, 3636-3641; Yuan et al 2000, Oncogene 19, 2324 – 2330), PKB alpha is amplified in human gastric, prostate and breast cancer (Staal 1987, PNAS 84, 5034 – 5037; Sun et al 2001, Am. J. Pathol. 159, 431 –437) and increased PKB gamma activity has been observed in steroid independent breast and prostate cell lines (Nakatani et al 1999, J. Biol. Chem. 274, 21528 – 21532).

The PKB pathway also functions in the growth and survival of normal tissues and may be regulated during normal physiology to control cell and tissue function. Thus disorders associated with undesirable proliferation and survival of normal cells and tissues may also benefit therapeutically from treatment with a PKB inhibitor. Examples of such disorders are disorders of immune cells associated with prolonged expansion and survival of cell population leading to a prolonged or up regulated immune response. For example, T and B lymphocyte response to cognate antigens or growth factors such as interleukin-2 activates the PI3K/PKB pathway and is responsible for maintaining the survival of the antigen specific lymphocyte clones during the immune response. Under conditions in which lymphocytes and other immune cells are responding to inappropriate self or foreign antigens, or in which other abnormalities lead to prolonged activation, the PKB pathway contributes an important survival signal preventing the normal mechanisms by which the immune response is terminated via apoptosis of the activated cell population. There is a considerable amount of evidence demonstrating the expansion of lymphocyte populations responding to self antigens in autoimmune conditions such as multiple sclerosis and arthritis. Expansion of lymphocyte populations responding inappropriately to foreign antigens is a feature of another set of conditions such as allergic responses and asthma. In summary inhibition of PKB could provide a beneficial treatment for immune disorders.

Other examples of inappropriate expansion, growth, proliferation, hyperplasia and survival of normal cells in which PKB may play a role include but are not limited to atherosclerosis, cardiac myopathy and glomerulonephritis.

In addition to the role in cell growth and survival, the PKB pathway functions in the control of glucose metabolism by insulin. Available evidence from mice deficient in the alpha and beta isoforms of PKB suggests that this action is mediated by the beta isoform. As a consequence, modulators of PKB activity may also find utility in diseases in which there is a dysfunction of glucose metabolism and energy storage such as diabetes, metabolic disease and obesity.

Cyclic AMP-dependent protein kinase (PKA) is a serine/threonine protein kinase that phosphorylates a wide range of substrates and is involved in the regulation of many cellular processes including cell growth, cell differentiation, ion-channel conductivity, gene transcription and synaptic release of neurotransmitters. In its inactive form, the PKA holoenzyme is a tetramer comprising two regulatory subunits and two catalytic subunits.

PKA acts as a link between G-protein mediated signal transduction events and the cellular processes that they regulate. Binding of a hormone ligand such as glucagon to a transmembrane receptor activates a receptor-coupled G-protein (GTP-binding and hydrolyzing protein). Upon activation, the alpha subunit of the G protein dissociates and binds to and activates adenylate cyclase, which in turn converts ATP to cyclic-AMP (cAMP). The cAMP thus produced then binds to the regulatory subunits of PKA leading to dissociation of the associated catalytic subunits. The catalytic subunits of PKA, which are inactive when associated with the regulatory sub-units, become active upon dissociation and take part in the phosphorylation of other regulatory proteins.

For example, the catalytic sub-unit of PKA phosphorylates the kinase Phosphorylase Kinase which is involved in the phosphorylation of Phosphorylase, the enzyme responsible for breaking down glycogen to release glucose. PKA is also involved in the regulation of glucose levels by phosphorylating and deactivating glycogen synthase. Thus, modulators of PKA activity (which modulators may increase or decrease PKA activity) may be useful in the treatment or management of diseases in which there is a dysfunction of glucose metabolism and energy storage such as diabetes, metabolic disease and obesity.

PKA has also been established as an acute inhibitor of T cell activation. Anndahl *et al,* have investigated the possible role of PKA type I in HIV-induced T cell dysfunction on the basis that T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by cAMP analogues than are normal T cells. From their studies, they concluded that increased activation of PKA type I may contribute to progressive T cell dysfunction in HIV infection and that PKA type I may therefore be a potential target for immunomodulating therapy.-Aandahl, E. M., Aukrust, P., Skålhegg, B. S., Müller, F., Frøland, S. S., Hansson, V., Taskén, K. *Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients. FASEB J.* 12, 855--862 (1998).

It has also been recognised that mutations in the regulatory sub-unit of PKA can lead to hyperactivation in endocrine tissue.

Because of the diversity and importance of PKA as a messenger in cell regulation, abnormal responses of cAMP can lead to a variety of human diseases such as irregular cell growth and proliferation (Stratakis, C.A.; Cho-Chung, Y.S.; Protein Kinase A and human diseases. *Trends Endrocri. Metab.* 2002, 13, 50-52). Over-expression of PKA has been observed in a variety of human cancer cells including those from ovarian, breast and colon

patients. Inhibition of PKA would therefore be an approach to treatment of cancer (Li, Q.; Zhu, G-D.; *Current Topics in Medicinal Chemistry*, 2002, 2, 939-971).

For a review of the role of PKA in human disease, see for example, *Protein Kinase A and Human Disease*, Edited by Constantine A. Stratakis, Annals of the New York Academy of Sciences, Volume 968, 2002, ISBN 1-57331-412-9.

<u>hERG</u>

In the late 1990s a number of drugs, approved by the US FDA, had to be withdrawn from sale in the US when it was discovered they were implicated in deaths caused by heart malfunction. It was subsequently found that a side effect of these drugs was the development of arrhythmias caused by the blocking of hERG channels in heart cells. The hERG channel is one of a family of potassium ion channels the first member of which was identified in the late 1980s in a mutant *Drosophila melanogaster* fruitfly (see Jan, L.Y. and Jan, Y.N. (1990). A Superfamily of Ion Channels. *Nature*, 345(6277):672). The biophysical properties of the hERG potassium ion channel are described in Sanguinetti, M.C., Jiang, C., Curran, M.E., and Keating, M.T. (1995). A Mechanistic Link Between an Inherited and an Acquired Cardiac Arrhythmia: HERG encodes the Ikr potassium channel. *Cell*, 81:299-307, and Trudeau, M.C., Warmke, J.W., Ganetzky, B., and Robertson, G.A. (1995). HERG, a Human Inward Rectifier in the Voltage-Gated Potassium Channel Family. *Science*, 269:92-95.

The elimination of hERG blocking activity remains an important consideration in the development of any new drug.

<u>Prior Art</u>

Several classes of compounds have been disclosed as having PKA and PKB inhibitory activity.

For example, a class of isoquinolinyl-sulphonamido-diamines having PKB inhibitory activity is disclosed in WO 01/91754 (Yissum).

WOO/07996 (Chiron) discloses substituted pyrazoles having estrogen receptor agonist activity. The compounds are described as being useful in treatingor preventing *inter alia* estrogen-receptor mediated breast cancer. PKB inhibitory activity is not disclosed.

WO 00/31063 (Searle) discloses substituted pyrazole compounds as p38 kinase inhibitors.

WO 01/32653 (Cephalon) discloses a class of pyrazolone kinase inhibitors.WO 03/059884 (X-Ceptor Therapeutics) discloses N-substituted pyridine compounds as modulators of nuclear receptors.

WO 03/068230 (Pharmacia) discloses substituted pyridones as p38 MAP kinase modulators.

WO 00/66562 (Dr Reddy's Research Foundation) discloses a class of 1-phenyl-substituted pyrazoles for use as anti-inflammatory agents. The 1-phenyl group is substituted by a sulphur-containing substituent as a sulphonamide or sulphonyl group.

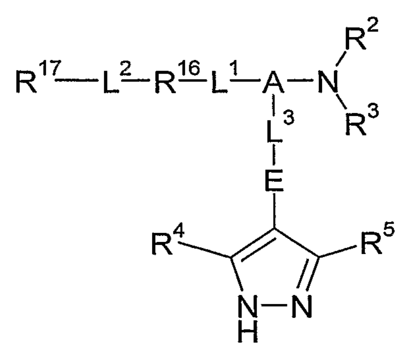
WO 00/14066 (Pfizer) and WO 00/39091 (Pfizer) each disclose a class of 4,4-diphenylpiperidine compounds having opioid receptor activity which are stated to be useful in treating neurological and gastrointestinal disorders, and various other diseases including inflammatory conditions such as psoriasis.

WO 2005/061463 (Astex) discloses a class of substituted pyrazole compounds having PKB and PKA inhibitory activity.

Summary of the Invention

The invention provides compounds that have protein kinase B (PKB) and protein kinase A (PKA) inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by PKB or PKA.

In a first aspect, the invention provides a compound of the formula (I):



(I)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, C_1-C_4 alkyl, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl and C_{1-4} hydrocarbyloxycarbonyl wherein the hydrocarbyl, acyl and hydrocarbyloxycarbonyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is

selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONR'-, -NR'CO-, -S-, -C(O)-, , C(S)-, $-NR^{11}-$, $C(=CHR^{11})$, -SO- and $-SO_2-$;

R' is hydrogen or methyl;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms a monocyclic or bicyclic 5-12 membered heteroaryl ring system;

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously;

R^{16} is a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, $-CONHR^{11}$, $-NHCOR^{11}$, $-C(O)OR^{11}$, COR^{11}, halogen, NO_2 or CN;

wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^{16} may themselves be further substituted by one or more substituents chosen from OH, -O(C_1-C_6 alkyl), -$CONHR^{11}$, $-NHCOR^{11}$, $-C(O)OR^{11}$, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above;

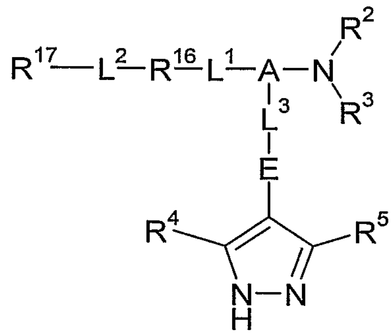
L^2 is absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -O-, -S-, -C(O)-, $C(=CHR^{11})$, C(S)-, $-NR^{11}-$, C_{3-4} cycloalkanediyl and $-SO_2-$;

R^{17} is absent or is C_{1-6} alkyl or a 5 to 12 membered saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, $-N(R^{11})_2$, $-CONHR^{11}$, $-NHCOR^{11}$, $-C(O)OR^{11}$, COR^{11}, halogen, NO_2, CN, R^q, OR^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon

atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent;

wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -$N(R^{11})_2$, -O(C_1-C_6 alkyl), -$CONHR^{11}$, -$NHCOR^{11}$, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

In a second aspect, the invention provides a compound of the formula (I^0):



(I^0)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, C_1-C_4 alkyl, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic

group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c;

L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONR'-, -NR'CO-, -S-, -C(O)-, $C(=CHR^{11})$, C(S)-, $-N(R^{11})_2$, -SO- and $-SO_2$-;

R' is hydrogen or methyl;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms an 8-12 membered fused bicyclic heteroaryl ring system;

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously;

R^{16} is a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN;

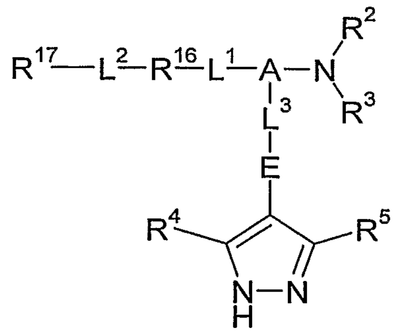
wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^{16} may themselves be further substituted by one or more substituents chosen from OH, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above;

L^2 is absent or is a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -O-, -S-, -C(O)-, C(=CHR^{11}), C(S)-, -N(R^{11})$_2$, C_{3-4} cycloalkanediyl and -SO_2-;

R^{17} is absent or is C_{1-6} alkyl or a 5 to 12 membered saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN, R^q, OR^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent;

wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -N(R^{11})$_2$, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

In another aspect, the invention provides a compound of the formula (Ia):



(Ia)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, C_1-C_4 alkyl, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

L^1 is a bond or a linker selected from -CONH-, -NHCO-, -C(O)-, -C(S)-, $-N(R^{11})_2$, -SO- and $-SO_2-$;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms an 8-12 membered fused bicyclic heteroaryl ring system;

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously;

R^{16} is a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, $-O(C_1$-C_6 alkyl), -OH, $-CONHR^{11}$, $-NHCOR^{11}$, $-C(O)OR^{11}$, COR^{11}, halogen, NO_2 or CN;

wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^{16} may themselves be further substituted by one or more substituents chosen from OH, $-O(C_1$-C_6 alkyl), $-CONHR^{11}$, $-NHCOR^{11}$, $-C(O)OR^{11}$, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above;

L^2 is absent or is a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONH-, -NHCO-, -O-, -S-, -C(O)-, -C(S)-, -$N(R^{11})_2$, -SO- and -SO_2-;

R^{17} is absent or is C_{1-6} alkyl or a 5- or 6-membered saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -$N(R^{11})_2$, -$CONHR^{11}$, -$NHCOR^{11}$, -$C(O)OR^{11}$, COR^{11}, halogen, NO_2, CN, R^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent;

wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -$N(R^{11})_2$, -O(C_1-C_6 alkyl), -$CONHR^{11}$, -$NHCOR^{11}$, -$C(O)OR^{11}$, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

The invention further provides:

- A compound *per se* of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any other sub-group or embodiment of the formula (I) as defined herein.

- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

- The use of a compound of formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

- A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, which method comprises administering to a subject in need thereof a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein.

- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI), or any sub-group thereof as defined herein for use in treating a disease or condition

comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal.

- The use of a compound of (I), (Ia), or any sub-group thereof as defined herein for the manufacture of a medicament for treating a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal.

- A method for treating a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal, the method comprising administering to the mammal a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein in an amount effective to inhibit protein kinase B activity.

- A method of inhibiting protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein.

- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a protein kinase B using a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein.

- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

- The use of a compound of formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

- A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A, which method comprises administering to a subject in need thereof a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein.

- A method for treating a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal, the method comprising

administering to the mammal a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein in an amount effective to inhibit protein kinase A activity.

- A method of inhibiting protein kinase A, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein.
- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a protein kinase A using a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein.
- The use of a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth or abnormally arrested cell death.
- A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein in an amount effective in inhibiting abnormal cell growth or abnormally arrested cell death.
- A method for alleviating or reducing the incidence of a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal, which method comprises administering to the mammal a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein in an amount effective in inhibiting abnormal cell growth.
- A pharmaceutical composition comprising a novel compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein and a pharmaceutically acceptable carrier.
- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for use in medicine.

- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for the prophylaxis or treatment of any one of the disease states or conditions disclosed herein.

- The use of a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of any one of the disease states or conditions disclosed herein.

- A method for the treatment or prophylaxis of any one of the disease states or conditions disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein.

- A method for alleviating or reducing the incidence of a disease state or condition disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein.

- A method for the diagnosis and treatment of a disease state or condition mediated by protein kinase B, which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against protein kinase B; and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein.

- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase B.

- The use of a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group thereof as defined herein for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase B.

- A method for the diagnosis and treatment of a disease state or condition mediated by protein kinase A, which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against protein kinase A; and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein.

- A compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase A.

- The use of a compound of the formula (I), (I^0), (Ia), (II), (III), (IV), (V), (VI) or any sub-group or embodiment thereof as defined herein for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase A.

<u>General Preferences and Definitions</u>

In this specification, the structural drawings have been prepared using the ISIS Draw Program. In certain cases, hydrogen atoms may not be shown but are merely implied. Thus, for example, some amino and hydroxy groups may appear simply as:

$$-\mathrm{N}- \quad , \quad -\mathrm{N} \quad \text{or} \quad -\mathrm{O}$$

Where such apparently incomplete structures are shown, they are to be interpreted as though the hydrogen atoms are present, unless the context requires otherwise.

The following general preferences and definitions shall apply to each of the moieties A, E, L^1, L^{1a}, L^{1b}, L^2, L^{2a}, L^3, R^2 to R^5, R^{4a}, R^{5a}, R^9 , R^{9a}, R^{11}, R^{16}, R^{17}, R^{17a}, R^a, R^b, R^c, R^q, X^1 and X^2 and any sub-definition, sub-group or embodiment thereof, unless the context indicates otherwise.

Any references to formulae (I), (I^0) and (Ia) herein shall be taken also to refer any sub-group of compounds within formulae (I), (I^0) and (Ia) unless the context requires otherwise.

References to "carbocyclic" and "heterocyclic" groups as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. In general, such groups may be monocyclic or bicyclic and may contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7, and 8 ring members, more usually 3 to 7, and preferably 5 or 6 ring members. Examples of bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members.

The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may be attached by the aromatic ring, or by a non-aromatic ring. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{10} as defined herein.

The term non-aromatic group embraces unsaturated ring systems without aromatic character, partially saturated and fully saturated carbocyclic and heterocyclic ring systems. The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a C=C, C≡C or N=C bond. The term "fully saturated" refers to rings where there are no multiple bonds between ring atoms. Saturated carbocyclic groups

include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cycloheptenyl and cyclooctenyl.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure (e.g. an 8-12 membered fused bicyclic heteroaryl ring system) formed from fused five and six membered rings or two fused six membered rings; or (in the case of eleven and twelve membered rings) an aromatic six membered ring fused to a seven membered or eight membered ring. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups.

Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

A bicyclic heteroaryl group may be, for example, a group selected from:

a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

b) a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

c) a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

d) a pyrrole ring fused to a a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

e) a pyrazole ring fused to a a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

f) a pyrazine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

g) an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

h) an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

i) an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

j) a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

k) an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

l) a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

m) a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

n) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and

o) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

Examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuran, benzthiophene, benzimidazole, benzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole and pyrazolopyridine groups.

Examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine,

pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline and indane groups.

It will be appreciated that the term “8-12 membered fused bicyclic heteroaryl ring system” as used herein encompasses each of the definitions, sub-groups, preferences and examples of bicyclic heteroaryl groups defined above and elsewhere herein.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur.

The heterocylic groups can contain, for example, cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulpholane and sulpholene), cyclic sulphoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine). Other examples of non-aromatic heterocyclic groups include cyclic amide moieties (e.g. as in pyrrolidone) and cyclic ester moieties (e.g. as in butyrolactone). Another example of a non-aromatic group is a cyclic urethane moiety such as an oxazolidin-2-one.

Examples of monocyclic non-aromatic heterocyclic groups include 5-, 6-and 7-membered monocyclic heterocyclic groups. Particular examples include morpholine, thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine), piperidine (e.g. 1-piperidinyl, 2-piperidinyl 3-piperidinyl and 4-piperidinyl), N-alkyl piperidines such as N-methyl piperidine, piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone,

oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine, N-ethyl piperazine and N-isopropylpiperazine.

One sub-group of monocyclic non-aromatic heterocyclic groups includes morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl 3-piperidinyl and 4-piperidinyl), piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include piperidine, pyrrolidine, azetidine, morpholine, piperazine and N-alkyl piperazines. A further particular example of a non-aromatic heterocyclic group, which also forms part of the above group of preferred non-aromatic heterocyclic groups, is azetidine.

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, as well as cyclohexadienyl, cyclooctatetraene, tetrahydronaphthenyl and decalinyl.

Each of the definitions of carbocyclic and heterocyclic groups in this specification may optionally exclude any one or any combination of two or more of the following moieties:
- substituted or unsubstituted pyridone rings;
- substituted or unsubstituted pyrrolo[1,2-a]pyrimid-4-ones;
- substituted or unsubstituted pyrazolones.

Where reference is made herein to carbocyclic and heterocyclic groups, the carbocyclic or heterocyclic ring can, unless the context indicates otherwise, be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members

and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

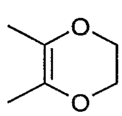
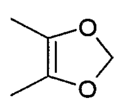
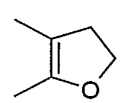
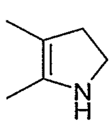
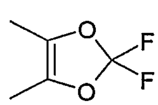
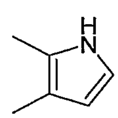
R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10}. In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10}.

The substituents R^{10} may be selected such that they contain no more than 20 non-hydrogen atoms, for example, no more than 15 non-hydrogen atoms, e.g. no more than 12, or 10, or 9, or 8, or 7, or 6, or 5 non-hydrogen atoms.

Where the carbocyclic and heterocyclic groups have a pair of substituents on adjacent ring atoms, the two substituents may be linked so as to form a cyclic group. For example, an adjacent pair of substituents on adjacent carbon atoms of a ring may be linked via one or more heteroatoms and optionally substituted alkylene groups to form a fused oxa-, dioxa-, aza-, diaza- or oxa-aza-cycloalkyl group. Examples of such linked substituent groups include:

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms. Examples of hydrocarbyl groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or, where stated, can be substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formulae (I) and (Ia) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2} hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 hydrocarbyl groups.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} alkyl groups, such as C_{1-4} alkyl groups (e.g. C_{1-3} alkyl groups or C_{1-2} alkyl groups).

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C_{3-6} cycloalkyl groups.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C_{2-6} alkenyl groups, such as C_{2-4} alkenyl groups.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C_{3-6} cycloalkenyl groups.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C_{2-6} alkynyl groups, such as C_{2-4} alkynyl groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl, naphthyl, indane and indene groups.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

The term C_{1-8} hydrocarbyl as used herein encompasses alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, phenyl, benzyl and phenylethyl groups wherein the preferences for and examples of each of the aforesaid groups are as defined above. Within this definition, particular hydrocarbyl groups are alkyl, cycloalkyl, phenyl, benzyl and phenylethyl (e.g. 1-phenylethyl or 2-phenylethyl) groups, one subset of hydrocarbyl groups consisting of alkyl and cycloalkyl groups and in particular C_{1-4} alkyl and cycloalkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, cyclopropyl and cyclobutyl.

The term C_{1-4} hydrocarbyl as used herein encompasses alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl groups wherein the preferences for and examples of the aforesaid groups are as defined above. Within this definition, particular C_{1-4} hydrocarbyl groups are alkyl and cycloalkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, cyclopropyl and cyclobutyl.

The term C_{1-5} saturated hydrocarbyl as used herein encompasses alkyl and cycloalkyl groups having 1 to 5 carbon atoms. Within this definition, particular C_{1-5} saturated hydrocarbyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, cyclopropyl and cyclobutyl.

When present, and where stated, a hydrocarbyl group can be optionally substituted by one or more substituents selected from hydroxy, oxo, alkoxy, carboxy, halogen, cyano, nitro,

amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic or bicyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituted hydrocarbyl group can be a partially fluorinated or perfluorinated group such as difluoromethyl or trifluoromethyl. In one embodiment preferred substituents include monocyclic carbocyclic and heterocyclic groups having 3-7 ring members.

Where stated, one or more carbon atoms of a hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ (or a sub-group thereof) wherein R^c, X^1 and X^2 are as hereinbefore defined, provided that at least one carbon atom of the hydrocarbyl group remains. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. In general, the number of linear or backbone carbon atoms replaced will correspond to the number of linear or backbone atoms in the group replacing them. Examples of groups in which one or more carbon atom of the hydrocarbyl group have been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C-C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2), amines (C replaced by NR^c). Further examples include ureas, carbonates and carbamates (C-C-C replaced by $X^1C(X^2)X^1$).

Where an amino group has two hydrocarbyl substituents, they may, together with the nitrogen atom to which they are attached, and optionally with another heteroatom such as nitrogen, sulphur, or oxygen, link to form a ring structure of 4 to 7 ring members.

The definition "R^a-R^b" as used herein, either with regard to substituents present on a carbocyclic or heterocyclic moiety, or with regard to other substituents present at other locations on the compounds of the formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, $C(S)NR^c$, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$, $SC(O)NR^c$, $NR^cC(O)$ NR^c, $OC(S)NR^c$, SC(S) NR^c, $NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^cNR^c$, S, SO, SO_2, NR^c, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined. Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

When R^a is O and R^b is a C_{1-8} hydrocarbyl group, R^a and R^b together form a hydrocarbyloxy group. Preferred hydrocarbyloxy groups include saturated hydrocarbyloxy such as alkoxy (e.g. C_{1-6} alkoxy, more usually C_{1-4} alkoxy such as ethoxy and methoxy, particularly methoxy), cycloalkoxy (e.g. C_{3-6} cycloalkoxy such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy) and cycloalkyalkoxy (e.g. C_{3-6} cycloalkyl-C_{1-2} alkoxy such as cyclopropylmethoxy).

The hydrocarbyloxy groups can be substituted by various substituents as defined herein. For example, the alkoxy groups can be substituted by halogen (e.g. as in difluoromethoxy and trifluoromethoxy), hydroxy (e.g. as in hydroxyethoxy), C_{1-2} alkoxy (e.g. as in methoxyethoxy), hydroxy-C_{1-2} alkyl (as in hydroxyethoxyethoxy) or a cyclic group (e.g. a cycloalkyl group or non-aromatic heterocyclic group as hereinbefore defined). Examples of alkoxy groups bearing a non-aromatic heterocyclic group as a substituent are those in which the heterocyclic group is a saturated cyclic amine such as morpholine, piperidine, pyrrolidine, piperazine, C_{1-4}-alkyl-piperazines, C_{3-7}-cycloalkyl-piperazines, tetrahydropyran or tetrahydrofuran and the alkoxy group is a C_{1-4} alkoxy group, more typically a C_{1-3} alkoxy group such as methoxy, ethoxy or n-propoxy.

Alkoxy groups may be substituted by, for example, a monocyclic group such as pyrrolidine, piperidine, morpholine and piperazine and N-substituted derivatives thereof such as N-benzyl, N-C_{1-4} acyl and N-C_{1-4} alkoxycarbonyl. Particular examples include pyrrolidinoethoxy, piperidinoethoxy and piperazinoethoxy.

When R^a is a bond and R^b is a C_{1-8} hydrocarbyl group, examples of hydrocarbyl groups R^a-R^b are as hereinbefore defined. The hydrocarbyl groups may be saturated groups such as cycloalkyl and alkyl and particular examples of such groups include methyl, ethyl and cyclopropyl. The hydrocarbyl (e.g. alkyl) groups can be substituted by various groups and atoms as defined herein. Examples of substituted alkyl groups include alkyl groups substituted by one or more halogen atoms such as fluorine and chlorine (particular examples including bromoethyl, chloroethyl, difluoromethyl, 2,2,2-trifluoroethyl and perfluoroalkyl groups such as trifluoromethyl), or hydroxy (e.g. hydroxymethyl and

hydroxyethyl), C_{1-8} acyloxy (e.g. acetoxymethyl and benzyloxymethyl), amino and mono- and dialkylamino (e.g. aminoethyl, methylaminoethyl, dimethylaminomethyl, dimethylaminoethyl and *tert*-butylaminomethyl), alkoxy (e.g. C_{1-2} alkoxy such as methoxy – as in methoxyethyl), and cyclic groups such as cycloalkyl groups, aryl groups, heteroaryl groups and non-aromatic heterocyclic groups as hereinbefore defined).

Particular examples of alkyl groups substituted by a cyclic group are those wherein the cyclic group is a saturated cyclic amine such as morpholine, piperidine, pyrrolidine, piperazine, C_{1-4}-alkyl-piperazines, C_{3-7}-cycloalkyl-piperazines, tetrahydropyran or tetrahydrofuran and the alkyl group is a C_{1-4} alkyl group, more typically a C_{1-3} alkyl group such as methyl, ethyl or n-propyl. Specific examples of alkyl groups substituted by a cyclic group include pyrrolidinomethyl, pyrrolidinopropyl, morpholinomethyl, morpholinoethyl, morpholinopropyl, piperidinylmethyl, piperazinomethyl and N-substituted forms thereof as defined herein.

Particular examples of alkyl groups substituted by aryl groups and heteroaryl groups include benzyl, phenethyl and pyridylmethyl groups.

When R^a is SO_2NR^c, R^b can be, for example, hydrogen or an optionally substituted C_{1-8} hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is SO_2NR^c include aminosulphonyl, C_{1-4} alkylaminosulphonyl and di-C_{1-4} alkylaminosulphonyl groups, and sulphonamides formed from a cyclic amino group such as piperidine, morpholine, pyrrolidine, or an optionally N-substituted piperazine such as N-methyl piperazine.

Examples of groups R^a-R^b where R^a is SO_2 include alkylsulphonyl, heteroarylsulphonyl and arylsulphonyl groups, particularly monocyclic aryl and heteroaryl sulphonyl groups. Particular examples include methylsulphonyl, phenylsulphonyl and toluenesulphonyl.

When R^a is NR^c, R^b can be, for example, hydrogen or an optionally substituted C_{1-8} hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is NR^c include amino, C_{1-4} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, *tert*-butylamino), di-C_{1-4} alkylamino (e.g. dimethylamino and diethylamino) and cycloalkylamino (e.g. cyclopropylamino, cyclopentylamino and cyclohexylamino).

Specific Embodiments and Preferences

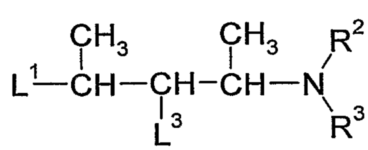
The Group "A"

In formula (I), A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, and wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group.

The term "saturated hydrocarbon" as used herein is used in its normal sense to denote a group formed from hydrogen and carbon atoms wherein the groups contains no multiple bonds (double or triple bonds) between adjacent carbon atoms.

The saturated hydrocarbon linker group can be acyclic or cyclic or can comprise both acyclic and cyclic hydrocarbon portions.

The term "maximum chain length" as used herein refers to the number of atoms lying directly between the two moieties in question, and does not take into account any branching in the chain or any hydrogen atoms that may be present. For example, in the structure A shown below:



(A)

the chain length between L^1 and NR^2R^3 is 3 atoms whereas the chain length between L^3 and NR^2R^3 is 2 atoms.

In general it is presently preferred that the linker group has a maximum chain length of 3 atoms (for example 1 or 2 atoms).

In one embodiment, the linker group has a chain length of 3 atoms extending between L^1 and NR^2R^3.

It is preferred that the linker group has a maximum chain length of 3 atoms extending between L^3 and NR^2R^3.

When a nitrogen atom or oxygen atom are present, it is preferred that the nitrogen or oxygen atom and the NR^2R^3 group are spaced apart by at least two intervening carbon atoms.

Typically, a hydroxy group, if present, is located at a position β with respect to the NR^2R^3 group. In general, no more than one hydroxy group will be present. Where fluorine is present, it may be present as a single fluorine substituent or may be present in a difluoromethylene or trifluoromethyl group, for example. In one embodiment, a fluorine atom is located at a position β with respect to the NR^2R^3 group.

It will be appreciated that that when an oxo group is present at the carbon atom adjacent the NR^2R^3 group, the compound of the formula (I) will be an amide.

In one embodiment of the invention, no fluorine atoms are present in the linker group A.

In another embodiment of the invention, no hydroxy groups are present in the linker group A.

In a further embodiment, no oxo group is present in the linker group A.

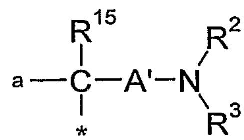
In one group of compounds of the formula (I) neither hydroxy groups nor fluorine atoms are present in the linker group A, e.g. the linker group A is unsubstituted.

Preferably, when a carbon atom in the linker group A is replaced by a nitrogen atom, the group A bears no more than one hydroxy substituent and more preferably bears no hydroxy substituents.

When a carbon atom in the linker group A is replaced by a nitrogen atom, it is preferred that the said nitrogen atom does not link directly to L^1 to form a urea group.

The linker group A can have a branched configuration at the carbon atom attached to the NR^2R^3 group. For example, the carbon atom attached to the NR^2R^3 group can be attached to a pair of *gem*-dimethyl groups.

In a preferred embodiment, the linker A has the formula:



wherein the points of attachment to L^1 and L^3 respectively are denoted by "a" and *.
A' is a linker as defined for A but which is up to 3 atoms in length (e.g. up to 2 atoms, for example 1 or 2); and
R^{15} is hydrogen, OH or C_1-C_4 alkyl or, with the carbon atom to which it is attached, the linker A', R^2 and the nitrogen atom to which it is attached forms a 5 to 7 membered heterocyclic ring which optionally contains one or more additional heteroatoms.

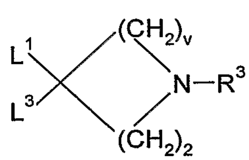
When R^{15} does not form part of a heterocyclic ring, it is preferred that it is hydrogen, OH or methyl.

In a particularly preferred group of compounds, within this embodiment, the linker group A' is one or two atoms in length. It is also preferred that it is a simple unsubstituted hydrocarbon chain, especially a saturated hydrocarbon chain, i.e. $-CH_2-$ or $-CH_2CH_2-$.

In a further particularly preferred group of compounds, the linker group A', together with the CR^{15} moiety and the NR^3 moiety form a 5 or 6 membered ring which may contain one or more additional heteroatoms.

Preferably, the ring of this type is a five or six membered ring which may contain one additional heteroatom, in particular an oxygen atom.

Thus, the linker group A may be of the formula:



wherein L^1, L^3 and NR^2R^3 are not part of the linker A but are included to show how it is linked to the rest of the molecule;
v is 1 or 2; and
any one of the CH_2 groups may be replaced by a heteroatom, for example O.

<u>L^3</u>

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously.

In a preferred embodiment, L^3 is a bond.

In another embodiment, L^3 is CONH or HNCO.

$\underline{L^1}$

L^1 is defined as a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, -C(S)-, $-N(R^{11})_2$, $C(=CHR^{11})$, -SO- and $-SO_2-$;

wherein R' is hydrogen or methyl, R^{11} is hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms a monocyclic or bicyclic 5-12 membered heteroaryl ring system.

When L^1 is –CONR'- or -NR'CO-, it is preferred that R' is hydrogen.

In one embodiment, L^1 is a bond or a linker selected from -CONH-, -NHCO-, -C(O)-, -C(S)-, $-N(R^{11})_2$, -SO- and $-SO_2-$;

wherein R^{11} is hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms a 8-12 membered fused heteroaryl ring system.

In another embodiment, L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, $C(=CHR^{11})$, -C(S)-, -SO- and $-SO_2-$;

wherein R' is hydrogen or methyl, R^{11} is hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms a 8-12 membered fused heteroaryl ring system.

In a further embodiment, L^1 is a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, $C(=CHR^{11})$, -C(S)-, -SO- and $-SO_2-$.

L^1 and L^3 cannot both be linkers simultaneously. When L^3 is a linker, L^1 is either a bond or, together with the group R^{16}, forms an 8-12 membered fused bicyclic heteroaryl ring system.

Also, L^1 and L^3 cannot both be a bond simultaneously.

When L^3 is a bond, L^1 is either a linker or, together with the group R^{16}, forms an 8-12 membered fused bicyclic heteroaryl ring system.

One group of preferred linkers L^1 consists of -CONH-, -NHCO-, -C(O)-, with -CONH-, and -NHCO- being particularly preferred.

In one general embodiment, L^1 is -CONH-.

In another general embodiment, L^1 is -NHCO-.

Another particular group of linkers L^1 consists of C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -C(O)- and C(=CHR^{11}).

When L^1 is C(=CHR^{11}), the group R^{11} is hydrogen or C_{1-6} alkyl. More typically, R^{11} is C_{1-4} alkyl, for example a *tert*-butyl group.

Examples of C_1-C_4 alkenylene linker groups are ethenylene (CH=CH), propenylene ($CH=CH-CH_2$) and butenylene ($CH_2-CH=CH-CH_2$ or $CH=CH-CH_2-CH_2$) in which R^{16} and A may be attached to either end of the linker. A preferred linker group is ethenylene (CH=CH).

Examples of C_1-C_4 alkynylene linker groups are ethynylene (CH≡CH), propynylene ($CH{\equiv}CH-CH_2$) and butynylene ($CH_2-CH{\equiv}CH-CH_2$ or $CH{\equiv}CH-CH_2-CH_2$) in which R^{16} and A may be attached to either end of the linker. A preferred linker group is ethynylene (CH≡CH).

In another preferred embodiment, L^1 and R^{16} combine to form a 8-12 membered (e.g. 8-10 membered) fused bicyclic heteroaryl ring system in which each ring is a 5 or 6 membered ring containing up to 3 nitrogen atoms and in which any of the ring CH groups can be replaced by C=O. Examples of such groups include indole, azaindole, purine and benzimidazole, with benzimidazole being particularly preferred. In a further example, L^1 and R^{16} combine to form a benzoxazole or benzothiazole group (and more preferably a benzoxazole group).

When L^1 and R^{16} combine to form a benzimidazole ring system, the linker A is preferably linked to the carbon atom between the two nitrogen atoms of the benzimidazole ring.

Similarly, when L^1 and R^{16} combine to form a benzoxazole or benzothiazole ring system, the linker A is preferably linked to the carbon atom between the nitrogen and oxygen/sulphur atoms of the benzoxazole/benzothiazole ring.

In another embodiment, L^1 and R^{16} combine to form a five or six membered heterocyclic ring system and more preferably a five membered heterocyclic ring system such as an imidazole or oxazole ring system. When the five membered ring system is an imidazole, it can be linked to the group A through either a nitrogen atom or a carbon atom.

$\underline{R^{16}}$

The group R^{16} is defined as a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH,
-CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN;
wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^1 may themselves be further substituted by one or more substituents chosen from OH, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above.

Suitable R^{16} groups may be selected from the list of such groups set out in the section headed General Preferences and Definitions.

As discussed above, R^{16} can also combine with L^1 to form a fused heteroaromatic ring system.

It is preferred that R^{16} is an aromatic group.

In one preferred embodiment, R^{16} is monocyclic. Particular examples of monocyclic aryl and heteroaryl groups are six membered aryl and heteroaryl groups containing up to 2 nitrogen ring members, and five membered heteroaryl groups containing up to 3 heteroatom ring members selected from O, S and N. Examples of such groups include phenyl, thiophene, furan, thiazole, imidazole, pyrimidine and pyridine.

In one sub-group of compounds, R^{16} is an aryl or heteroaryl group selected from phenyl, thienyl, furan, pyrimidine and pyridine.

In one preferred embodiment, R^{16} is a phenyl group.

In a further embodiment, R^{16} is bicyclic. Particularly suitable examples of bicyclic aryl and heteroaryl groups contain up to two nitrogen ring members and consist of two fused six

membered rings or a 6-membered ring fused to a 5-membered ring. One particular example of such a ring system is benzooxazole, and in particular 2-benzooxazole.

The group R^{16} (whether or not combined with the linker L^1) can be unsubstituted or substituted by up to 5 substituents, as listed above. Preferred substituents, however, are halogen, -O(C_1-C_4 alkyl), -O(C_1-C_4 haloalkyl) and hydroxy, with chlorine, fluorine, methoxy and hydroxy being particularly preferred.

Although up to 5 substituents may be present, more typically there are 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1 or 2.

$\underline{L^2}$

L^2 is can be absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -O-, -S-, -C(O)-, -C(S)-, -N(R^{11})$_2$, C(=CHR^{11}), C_{3-4} cycloalkanediyl, -SO- and -SO_2-;_wherein R' is hydrogen or methyl (preferably hydrogen), R^{11} is hydrogen or C_1-C_6 alkyl.

When R^{17} is absent, L^2 is also absent, but when R^{17} is present, L^2 can be a bond or a linker.

In one embodiment, L^2 is a linker.

When L^2 is –CONR'- or -NR'CO-, it is preferred that R' is hydrogen.

In one group of compounds, L^2 is absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONH-, -NHCO-, -O-, -S-, -C(O)-, -C(S)-, -N(R^{11})$_2$, -SO- and -SO_2-.

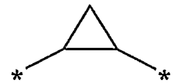
In one preferred group of compounds of formula (I), L^2 is -C(O)-, -O-, -S-, -SO- or -SO_2-. It is especially preferred that L^2 is C(O)-, -O- or -SO_2-.

In another preferred embodiment, L^2 is a bond and R^{17} is directly linked to R^{16}.

Particular and preferred C_1-C_4 alkenylene and C_1-C_4 alkynylene groups are as defined in respect of the linker group L^1 above.

The C_{3-4} cycloalkanediyl linkers can be either cyclopropanediyl or cyclobutanediyl groups. Examples of such groups are:

cyclopropane-1,1-diyl



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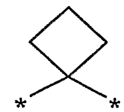
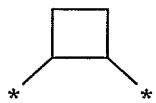


cyclobutane-1,1-diyl



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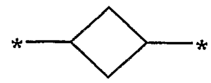


cyclobutane-1,3-diyl

The asterisks shown the points of attachment to R^{16} and R^{17}.

Preferred C_{3-4} cycloalkanediyl linkers are cyclopropane-1,1-diyl and cyclopropane-1,2-diyl, and in particular cyclopropane-1,2-diyl.

When L^2 is C_1-C_4 alkylene, the C_1-C_4 alkylene group can be straight chain or branched alkylene. Particular alkylene groups are methylene (CH_2) and ethylene (CH_2CH_2).

When L^2 is C(=CHR^{11}), the group R^{11} is hydrogen or C_{1-6} alkyl. More typically, R^{11} is C_{1-4} alkyl, for example a *tert*-butyl group.

<u>R^{17}</u>

In formula (I), R^{17} is absent or is C_{1-6} alkyl or a 5 to 12 membered (e.g. 5- or 6-membered) saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN, R^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent; wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -N(R^{11})$_2$, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

In one group of preferred compounds of formula (I), R^{17} is a 5- or 6-membered aryl or heteroaryl group or a 5- or 6-membered cycloalkyl or heterocyclyl group. Examples of such groups are listed in the section headed General Preferences and Definitions.

In one particular group of compounds, particularly suitable R^{17} groups include 6-membered ring systems such as phenyl, pyridyl, morpholinyl, piperidinyl and piperazinyl.

In another group of compounds, R^{17} groups include 6-membered ring systems such as phenyl, pyrimidinyl, pyridyl, pyridazinyl, morpholinyl, piperidinyl and piperazinyl; five membered ring systems such as pyrazolyl, oxazolyl, triazolyl and tetrazolyl; and 5.6 fused bicyclic ring systems such as benzoxazolyl.

In another group of compounds, R^{17} groups include 6-membered ring systems such as phenyl, pyrimidinyl, pyridyl, pyridazinyl, morpholinyl, piperidinyl and piperazinyl; five membered ring systems such as pyrazolyl, oxazolyl, thiazolyl, imidazolyl, oxazolidinone, triazolyl and tetrazolyl; and 5.6 fused bicyclic ring systems such as benzoxazolyl.

In further embodiments, each of the aforementioned groups of compounds can also include compounds wherein R^{17} is an oxazolidinone ring, e.g. an oxazolidin-2-one.

R^{17} may be unsubstituted or may be substituted with up to 5 of the substituents listed above.

In one group of compounds, R^{17} is unsubstituted or is substituted with halogen, hydroxy, -$N(R^{11})_2$, -O(C_1-C_4 alkyl), -O(C_1-C_4 haloalkyl), -O(C_1-C_4 alkyl)-O(C_1-C_4 alkyl), -O(C_{5-6} carbocyclyl), -O(c_{5-6} heterocyclyl), a 5- or 6-membered carbocyclic or heterocyclic ring, -C_1-C_4 alkyl(carbocyclyl)or -C_1-C_4 alkyl(heterocyclyl).

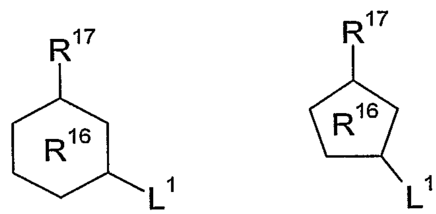
Within this group of compounds, particular examples of such substituents include chlorine, fluorine, hydroxy, methoxy, ethoxy, isopropyloxy, n-propyloxy, cyclopentyloxy, morpholinyl, piperidinyl, 3,3-dimethylpiperidin-1-yl, 4-methyl-piperazin-1-yl, -OCH_2-OCH_3, dimethylamino, trifluoromethoxy, -CH_2-(morpholinyl), -CH_2-(piperazinyl), -CH_2-(N-piperidinyl), -CH_2-(4-methyl-piperazin-1-yl) or CH_2-(cyclopentyl).

In another group of compounds, R^{17} is unsubstituted or is substituted with halogen (e.g. fluorine or chlorine), C_{1-4} alkyl (e.g. methyl), halo- C_{1-4} alkyl (e.g. trifluoromethyl), C_{3-7} cycloalkyl, hydroxy, -$N(R^{11})_2$, -O(C_1-C_4 alkyl) (e.g. methoxy), -O(C_1-C_4 haloalkyl), -O(C_1-C_4 alkyl)-O(C_1-C_4 alkyl), -O(C_{5-6} carbocyclyl), -O(c_{5-6} heterocyclyl), a 5- or 6-membered carbocyclic or heterocyclic ring, -C_1-C_4 alkyl(carbocyclyl)or -C_1-C_4 alkyl(heterocyclyl).

More preferred compounds have an R^{17} group with 0 to 3 substituents.

In one sub-group of compounds of the formula (I), R^{16} is a monocyclic aryl or heteroaryl group and R^{17} is directly attached to R^{16} at a ring position which is *meta* relative to the point of attachment of R^{16} to L^1.

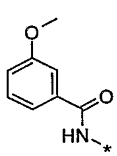
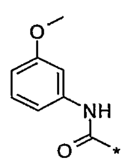
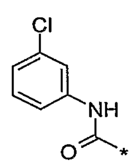
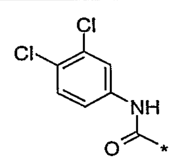
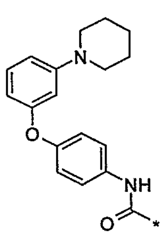
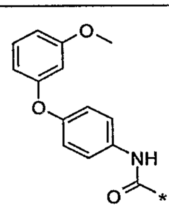
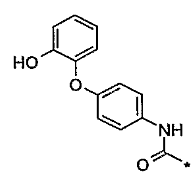
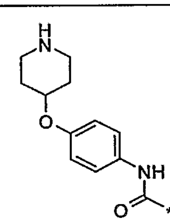
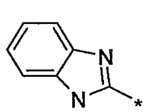
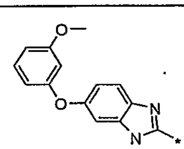
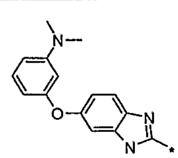
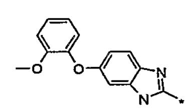
In the case of five and six membered aryl or heteroaryl rings, the term *meta* as used herein with reference to R^{16}, R^{17} and L^1 refers to the following relative orientations of R^{16}, R^{17} and L^1.

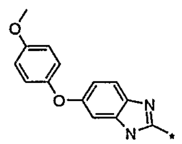
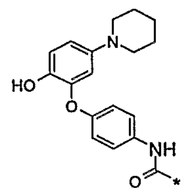
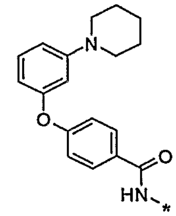
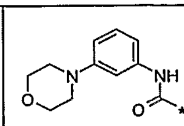
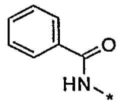
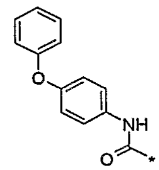
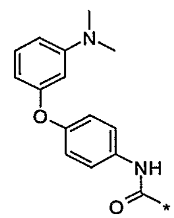
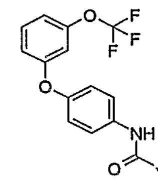
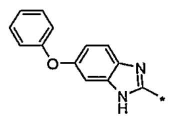
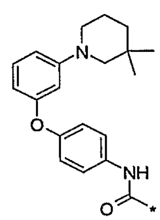
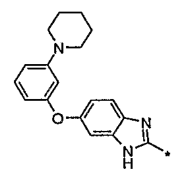
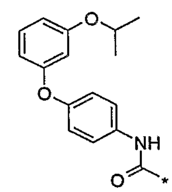
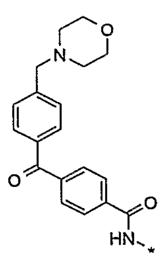
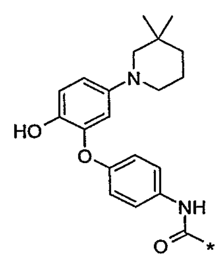
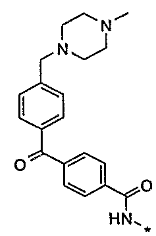
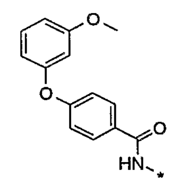
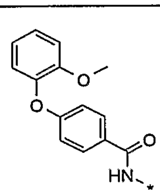
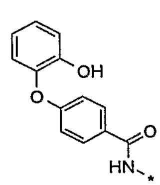
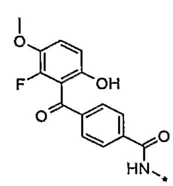
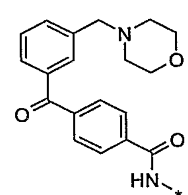


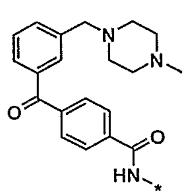
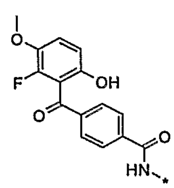
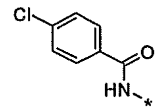
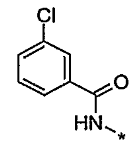
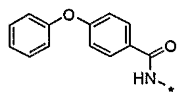
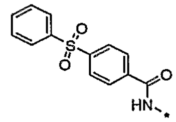
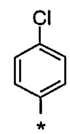
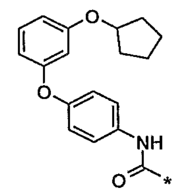
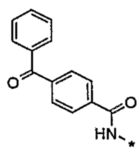
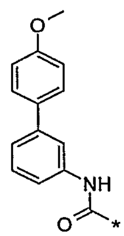
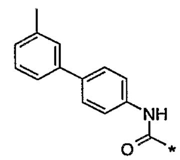
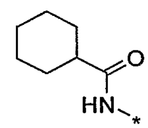
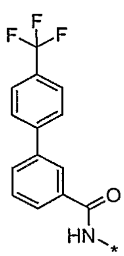
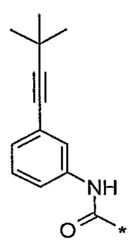
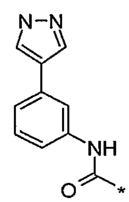
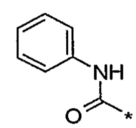
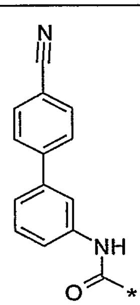
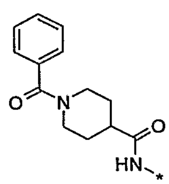
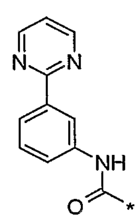
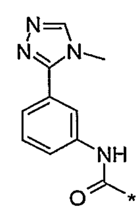
In another group of compounds of formula (I), R^{17} and L^2 are both absent.

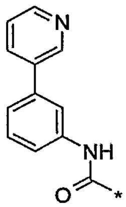
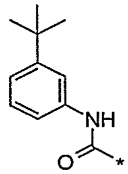
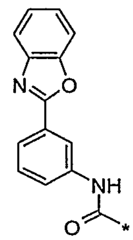
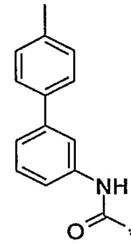
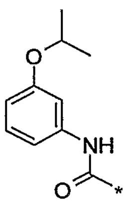
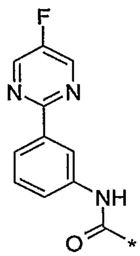
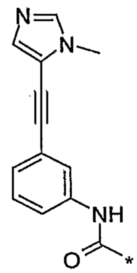
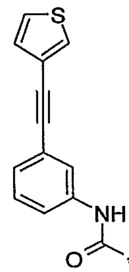
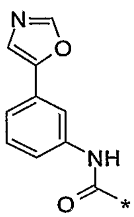
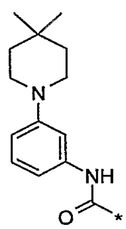
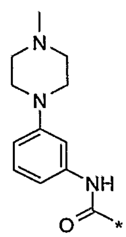
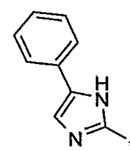
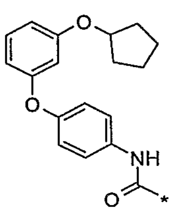
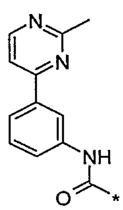
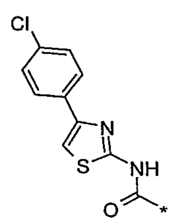
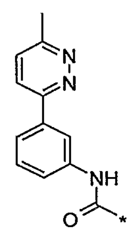
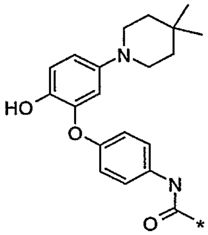
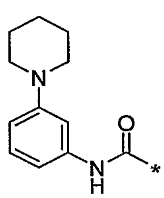
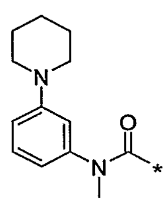
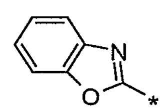
Particular examples of the moiety R^{17}-L^2-R^{16}-L^1 are set out in Table 1 below. The point of attachment to the moiety A is indicated by the asterisk.

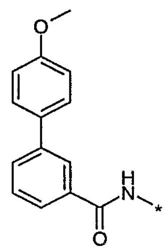
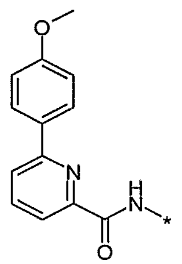
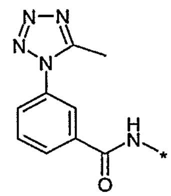
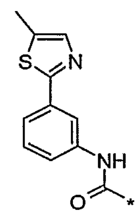
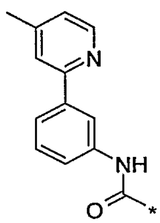
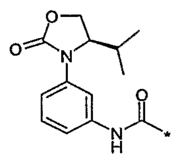
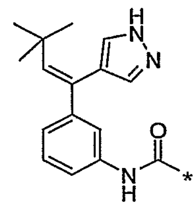
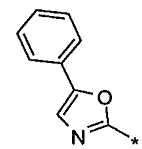
<u>Table 1</u>

 A1	 A2	 A3	 A4
 A5	 A6	 A7	 A8
 A9	 A10	 A11	 A12

 A13	 A14	 A15	 A16
 A17	 A18	 A19	 A20
 A21	 A22	 A23	 A24
 A25	 A26	 A27	 A28
 A29	 A30	 A31	 A32

 A33	 A34	 A35	 A36
 A37	 A38	 A39	 A40
 A41	 A42	 A43	 A44
 A45	 A46	 A47	 A48
 A49	 A50	 A51	 A52

 A53	 A54	 A55	 A56
 A57	 A58	 A59	 A60
 A61	 A62	 A63	 A64
 A65	 A66	 A67	 A68
 A69	 A70	 A71	 A72

 A73	 A74	 A75	 A76
 A77	 A78	 A79	 A80

One subset of examples of the moiety R^{17}-L^2-R^{16}-L^1 consists of the groups A1 to A42, A46, A49, A56, A59, A62, A63 and A69.

Another sub-set of examples of the moiety R^{17}-L^2-R^{16}-L^1 consists of the groups A46, A51, A53, A55, A58, A62, A64, A68 and A72.

A preferred sub-set of examples of the moiety R^{17}-L^2-R^{16}-L^1 consists of the groups A55, A58 and A64.

A further preferred sub-set of examples of the moiety R^{17}-L^2-R^{16}-L^1 consists of the groups A58 and A64.

<u>R^2 and R^3</u>

In one group of compounds, R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl and C_{1-4} hydrocarbyloxycarbonyl wherein the hydrocarbyl, acyl and hydrocarbyloxycarbonyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy.

In another group of compounds of the formula (I), R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties

are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy.

When the hydrocarbyl moiety is substituted by a hydroxy, amino, methylamino, dimethylamino or methoxy group, typically there are at least two carbon atoms between the substituent and the nitrogen atom of the group NR^2R^3. Particular examples of substituted hydrocarbyl groups are hydroxyethyl and hydroxypropyl.

In another group of compounds of the invention, R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl.

Typically the hydrocarbyl group, whether substituted or unsubstituted, is an alkyl group, more usually a C_1, C_2 or C_3 alkyl group, and preferably a methyl group. In one particular sub-group of compounds, R^2 and R^3 are independently selected from hydrogen and methyl and hence NR^2R^3 can be an amino, methylamino or dimethylamino group. In one particular embodiment, NR^2R^3 can be an amino group. In another particular embodiment, NR^2R^3 can be a methylamino group.

In an alternative embodiment, the C_{1-4} hydrocarbyl group can be a cyclopropyl, cyclopropylmethyl or cyclobutyl group.

Typically, no more than one of R^2 and R^3 will be a C_{1-4} hydrocarbyloxycarbonyl group. When present, the C_{1-4} hydrocarbyloxycarbonyl group is preferably a saturated group, i.e. it contains no carbon-carbon multiple (e.g. double) bonds. Thus, for example, it can be an alkoxycarbonyl, cycloalkyloxycarbonyl or cyclopropylmethoxycarbonyl group. A particular example of an alkoxycarbonyl group is *tert*-butoxycarbonyl (boc).

In another group of compounds, R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

In a further group of compounds, R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

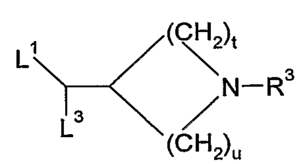
The saturated monocyclic heterocyclic group can be unsubstituted or substituted by one or more substituents R^{10} as defined above in the General Preferences and Definitions section of this application. Typically, however, any substituents on the heterocyclic group will be relatively small substituents such as C_{1-4} hydrocarbyl (e.g. methyl, ethyl, *n*-propyl, *i*-propyl, cyclopropyl, *n*-butyl, *sec*-butyl and *tert*-butyl), fluorine, chlorine, hydroxy, amino, methylamino, ethylamino and dimethylamino. Particular substituents are methyl groups.

The saturated monocyclic ring can be an azacycloalkyl group such as an azetidine, pyrrolidine, piperidine or azepane ring, and such rings are typically unsubstituted. Alternatively, the saturated monocyclic ring can contain an additional heteroatom selected from O and N, and examples of such groups include morpholine and piperazine. Where an additional N atom is present in the ring, this can form part of an NH group or an N-C_{1-4}alkyl group such as an N-methyl, N-ethyl, N-propyl or N-isopropyl group.

Where NR^2R^3 forms an imidazole group, the imidazole group can be unsubstituted or substituted, for example by one or more relatively small substituents such as C_{1-4} hydrocarbyl (e.g. methyl, ethyl, propyl, cyclopropyl and butyl), fluorine, chlorine, hydroxy, amino, methylamino, ethylamino and dimethylamino. Particular substituents are methyl groups.

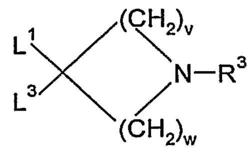
In a further group of compounds, one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

Examples of such compounds include compounds wherein NR^2R^3 and A form a unit of the formula:



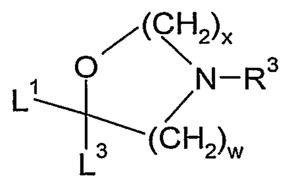
where t and u are each 0, 1, 2 or 3 provided that the sum of t and u falls within the range of 2 to 4.

Further examples of such compounds include compounds wherein NR^2R^3 and A form a cyclic group of the formula:



where v and w are each 0, 1, 2 or 3 provided that the sum of v and w falls within the range of 2 to 5. Particular examples of cyclic compounds are those in which v and w are both 2.

Further examples of such compounds include compounds wherein NR^2R^3 and A form a cyclic group of the formula:



where x and w are each 0, 1, 2 or 3 provided that the sum of x and w falls within the range of 2 to 4. Particular examples of cyclic compounds are those in which x is 2 and w is 1.

In each of the foregoing embodiments wherein NR^2R^3 and A form a cyclic group, R^3 can be hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl or C_{1-4} hydrocarbyloxycarbonyl as defined herein.

In each of the above examples, the linkers L^1 and L^3 are shown in order to illustrate the manner in which A is linked to the remainder of the molecule. It is not intended to imply that L^1 and L^3 form part of the moiety A as such.

$\underline{R^4}$

In formula (I), R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3.

More typically, R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano and CF_3. Preferred values for R^4 include hydrogen, methyl and ethyl. In one particular embodiment, R^4 is hydrogen or methyl. In another particular embodiment, R^4 is hydrogen.

$\underline{R^5}$

In formula (I), R^5 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$; $NHCONHR^9$ where R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is an

optionally substituted monocyclic or bicyclic group which may be carbocyclic or heterocyclic.

Examples of carbocyclic and heterocyclic groups are set out above in the General Preferences and Definitions section.

Typically the carbocyclic and heterocyclic groups are monocyclic.

Preferably the carbocyclic and heterocyclic groups are aromatic.

Particular examples of the group R^9 are optionally substituted phenyl or benzyl.

Preferably, R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

More preferably, R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

The group R^9 is typically unsubstituted phenyl or benzyl, or phenyl or benzyl substituted by 1,2 or 3 substituents selected from halogen; hydroxy; trifluoromethyl; cyano; carboxy; C_{1-4}alkoxycarbonyl; C_{1-4} acyloxy; amino; mono- or di-C_{1-4} alkylamino; C_{1-4} alkyl optionally substituted by halogen, hydroxy or C_{1-2} alkoxy; C_{1-4} alkoxy optionally substituted by halogen, hydroxy or C_{1-2} alkoxy; phenyl, five and six membered heteroaryl groups containing up to 3 heteroatoms selected from O, N and S; and saturated carbocyclic and heterocyclic groups containing up to 2 heteroatoms selected from O, S and N.

Particular examples of the moiety R^5 include hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9b}$ and $NHCONHR^{9b}$ where R^{9b} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy (e.g. alkoxy) and C_{1-4} hydrocarbyl (e.g. alkyl) optionally substituted by C_{1-2} alkoxy or hydroxy.

One set of preferred examples of R^5 consists of hydrogen, methyl, ethyl and cyano.

Another set of preferred examples of R^5 consists of hydrogen, methyl and cyano.

Preferably R^5 is hydrogen, methyl or ethyl and more particularly R^5 is hydrogen or methyl.

More preferably, R^4 is hydrogen or methyl when R^5 is hydrogen; and R^4 is hydrogen when R^5 is hydrogen or methyl.

<u>The Group "E"</u>

In formula (I), E is a monocyclic or bicyclic carbocyclic or heterocyclic group and can be selected from the groups set out above in the section headed General Preferences and Definitions.

Preferred groups E are monocyclic and bicyclic aryl and heteroaryl groups and, in particular, groups containing a six membered aromatic or heteroaromatic ring such as a phenyl, pyridine, pyrazine, pyridazine or pyrimidine ring, more particularly a phenyl, pyridine, pyrazine or pyrimidine ring, and more preferably a pyridine or phenyl ring.

Examples of bicyclic groups include benzo-fused and pyrido-fused groups wherein the group A and the pyrazole ring are both attached to the benzo- or pyrido- moiety.

In one embodiment, E is a monocyclic group.

Particular examples of monocyclic groups include monocyclic aryl and heteroaryl groups such as phenyl, thiophene, furan, pyrimidine, pyrazine and pyridine, phenyl being presently preferred.

One subset of monocyclic aryl and heteroaryl groups comprises phenyl, thiophene, furan, pyrimidine and pyridine.

Examples of non-aromatic monocyclic groups include cycloalkanes such as cyclohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone.

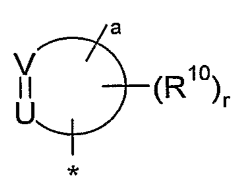
It is preferred that the group A and the pyrazole group are not attached to adjacent ring members of the group E. For example, the pyrazole group can be attached to the group E in a *meta* or *para* relative orientation. Examples of such groups E include 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl. Further examples include 1,3-disubstituted five membered rings .

The groups E can be unsubstituted or can have up to 4 substituents R^8 which may be selected from the group R^{10} as hereinbefore defined. More typically however, the substituents R^8 are selected from hydroxy; oxo (when E is non-aromatic); halogen (e.g. chlorine and bromine); trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy optionally substituted by C_{1-2} alkoxy or hydroxy; and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

Preferably there are 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent. In one embodiment, the group E is unsubstituted.

E may be other than:
- a substituted pyridone group;
- a substituted thiazole group;
- a substituted or unsubstituted pyrazole or pyrazolone group;
- a substituted or unsubstituted bicyclic fused pyrazole group;
- a phenyl ring fused to a thiophene ring or a six membered nitrogen-containing heteroaryl ring fused to a thiophene ring;
- a substituted or unsubstituted piperazine group;

The group E can be an aryl or heteroaryl group having five or six members and containing up to three heteroatoms selected from O, N and S, the group E being represented by the formula:

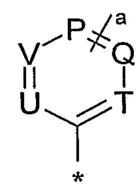


where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;
r is 0, 1 or 2;
U is selected from N and CR^{12a}; and
V is selected from N and CR^{12b}; where R^{12a} and R^{12b} are the same or different and each is hydrogen or a substituent containing up to ten atoms selected from C, N, O, F, Cl and S provided that the total number of non-hydrogen atoms present in R^{12a} and R^{12b} together does not exceed ten;

or R^{12a} and R^{12b} together with the carbon atoms to which they are attached form an unsubstituted five or six membered saturated or unsaturated ring containing up to two heteroatoms selected from O and N; and

R^{10} is as hereinbefore defined.

In one preferred group of compounds, E is a group:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

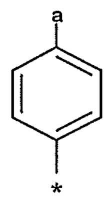
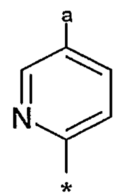
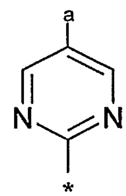
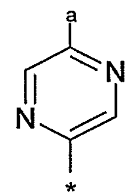
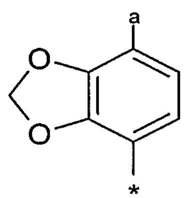
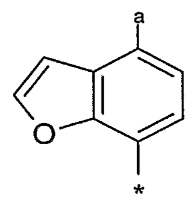
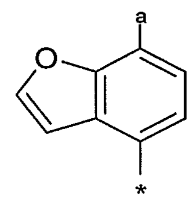
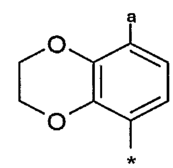
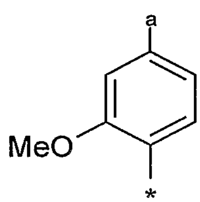
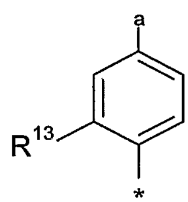
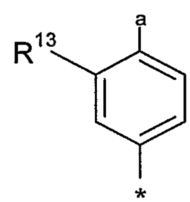
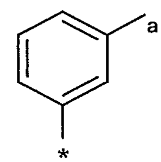
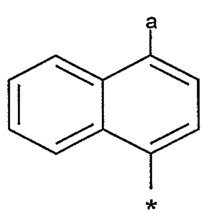
P, Q and T are the same or different and are selected from N, CH and NCR^{10}, provided that the group A is attached to a carbon atom; and U, V and R^{10} are as hereinbefore defined.

Examples of R^{12a} and R^{12b} include hydrogen and substituent groups R^{10} as hereinbefore defined having no more than ten non-hydrogen atoms. Particular examples of R^{12a} and R^{12b} include methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, fluorine, chlorine, methoxy, trifluoromethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethyl, cyano, amino, methylamino, dimethylamino, $CONH_2$, CO_2Et, CO_2H, acetamido, azetidinyl, pyrrolidino, piperidine, piperazino, morpholino, methylsulphonyl, aminosulphonyl, mesylamino and trifluoroacetamido.

Preferably, when U is CR^{12a} and/or V is CR^{12b} the atoms or groups in R^{12a} and R^{12b} that are directly attached to the carbon atom ring members C are selected from H, O (e.g. as in methoxy), NH (e.g. as in amino and methylamino) and CH_2 (e.g. as in methyl and ethyl).

Particular examples of the linker group E, together with their points of attachment to the carbon adjacent the group A (^{a}) and the pyrazole ring (*) are shown in Table 2 below.

<u>Table 2:</u>

 B1	 B2	 B3	 B4
 B5	 B6	 B7	 B8
 B9	 B10	 B11	 B12
 B13			

In the table, the substituent group R^{13} is selected from methyl, chlorine, fluorine and trifluoromethyl.

Preferred groups E are groups B1 and B12, of which B1 is more preferred.

The following optional exclusions may apply to the definition of E in formula (I) and any sub-groups or sub-definitions thereof as defined herein:

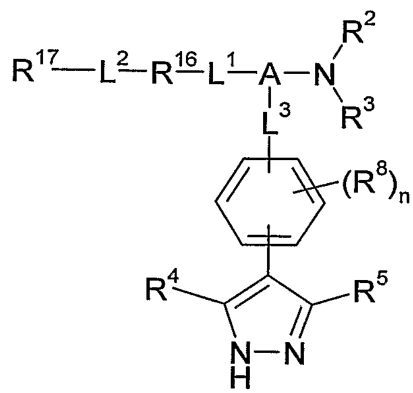
- E may be other than a phenyl group having a sulphur atom attached to the position *para* with respect to the pyrazole group.

- E may be other than a substituted or unsubstituted benzimidazole, benzoxazole or benzthiazole group.

In one sub-group of compounds of the formula (I), E is a benzene ring with the group A attached to the *meta* or *para* position, and there are 0-4 substituents R^8 on the benzene ring. In such compounds, q is preferably 0, 1 or 2, more preferably 0 or 1 and most preferably 0. Preferably the group A is attached to the *para* position of the benzene ring.

<u>Particular and Preferred Sub-Groups of Compounds</u>

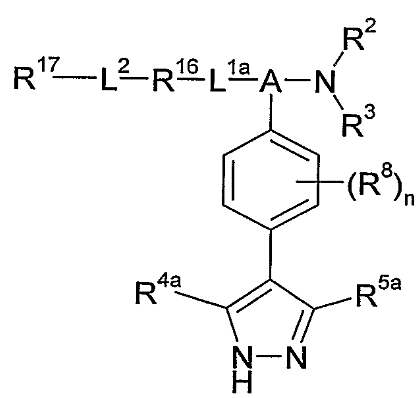
One particular group of compounds of the invention can be represented by the formula (II):



(II)

or a salt, solvate or tautomer thereof.

Within formula (II), one sub-group of compounds can be represented by the formula (III):

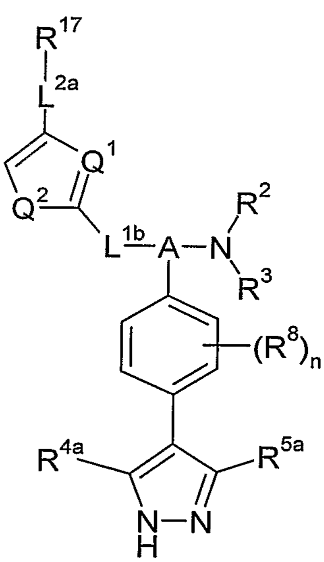


(III)

wherein R^{4a} is selected from hydrogen, halogen, methyl, methoxy, cyano, and CF_3; R^{5a} is selected from hydrogen, halogen, methyl, methoxy, cyano, CF_3 and $CONH_2$; and L^{1a} is selected from C(O)NH and NHC(O) or, together with the group R^{16} forms an 8-12 membered fused bicyclic heteroaryl ring system selected from benzoimidazole and benzoxazole; n is 0, 1 or 2 and A, R^2, R^3, R^8 and R^{17} are as defined herein.

In one preferred sub-set of compounds of formula (III), R^{16} is a five or six membered aryl or heteroaryl group, and more particularly may be a phenyl group, pyridyl group or a five membered heteroaryl ring containing up to two heteroatoms selected from O, N and S. Particular five membered heteroaryl rings are imidazole, thiazole and thiophene.

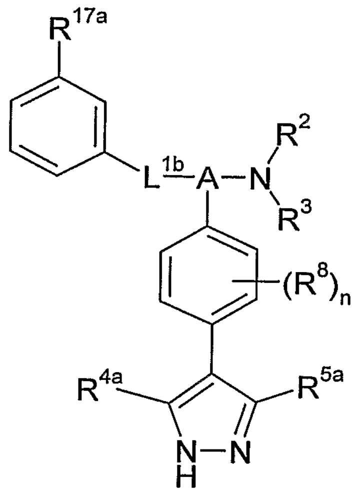
Accordingly, in one embodiment within formula (III), the compounds are represented by formula (IV):



(IV)

wherein L^{1b} is NHC(O) or C(O)NH; L^{2a} is bond or an ethynylene group; Q^1 is CH or N; Q^2 is CH=CH or S; and n, A, R^2, R^3, R^{4a}, R^{5a}, R^8 and R^{17} are as defined herein.

In another embodiment, the invention provides a sub-group of compounds within formula (IV) having the formula (V):



(V)

wherein R^{17a} is selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, piperidinyl, piperazinyl, pyrazolyl, oxazolyl, triazolyl, tetrazolyl, thiazolyl, oxo-oxazolidinyl, and benzoxazolyl, each optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN, R^q, OR^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring;
wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17a} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -N(R^{11})$_2$, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above, and n, A, R^2, R^3, R^{4a}, R^{5a} and R^8 are as defined herein.

More particularly, the substituents for R^{17a} are selected from halogen, trifluoromethyl, C_1-C_6 alkyl, and -O(C_1-C_6 alkyl).

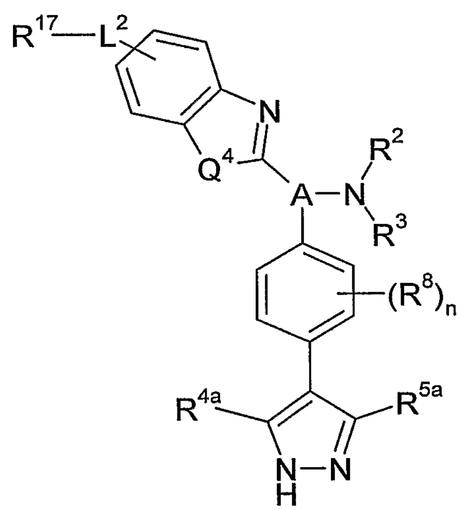
Preferably there are 0-2 substituents present on R^{17a}.

In one embodiment, R^{17a} is an unsubstituted group.

In another embodiment, R^{17a} is unsubstituted or is substituted by a single substituent selected from chlorine, fluorine, methyl, methoxy and trifluoromethyl.

In one sub-group of compounds within formula (V), R^{17a} is selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, piperidinyl, piperazinyl, pyrazolyl, oxazolyl, triazolyl, tetrazolyl, benzoxazolyl, each optionally substituted as hereinbefore defined.

Another particular sub-group of compounds of the invention can be represented by the formula (VI):



(VI)

wherein Q^4 is NH, S or O and A, n, L^2, R^2, R^3, R^{4a}, R^{5a}, R^8 and R^{17} are as defined herein.

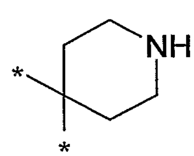
Preferably Q^4 is NH or O.

In one group of compounds within formula (VI), L^2 is O, or L^2 is a bond and R^{17} is absent.

In each of formulae (III), (IV), (V) and (VI), R^{4a} is preferably selected from hydrogen and methyl, and more preferably is hydrogen.

Also within each of formulae (III), (IV), (V) and (VI), R^{5a} is preferably selected from hydrogen and methyl, and more preferably is hydrogen. Preferably both R^{4a} and R^{5a} are hydrogen.

Also within each of formulae (III), (IV), (V) and (VI), the moiety A-NR^2R^3 may form the group:



where the asterisks indicate the points of attachment to the groups E (the benzene ring) and $L1/L^{1a}/L^{1b}$.

In each of formula (III), (IV), (V) and (VI), n can be 0, 1 or 2 but more preferably is 0 or 1 and most preferably is 0. When present (e.g. when n is 1), R^8 may be as defined above but preferably is a small substituent such as methyl, methoxy, fluorine, chlorine, cyano or trifluoromethyl.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example of the groups R^1 may be combined with each general and specific preference, embodiment and example of the groups R^2 and/or R^3 and/or R^4 and/or R^5 and/or R^9 and that all such combinations are embraced by this application.

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

Particular compounds of the invention are as illustrated in the examples below and are selected from:

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-3-methoxy-benzamide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-methoxy-phenyl)-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-chloro-phenyl)-amide;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3,4-dichloro-phenyl)-amide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-piperidin-1-yl-phenoxy)-phenyl]-amide diacetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-methoxy-phenoxy)-phenyl]-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(2-hydroxy-phenoxy)-phenyl]-amide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(piperidin-4-yloxy)-phenyl]-amide tritrifluoroacetate;
2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diacetate

6-(3-methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diformate;
dimethyl-[3-(2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-3H-benzoimidazol-5-yloxy)-phenyl]-amine diformate;
6-(2-methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole acetate;
6-(4-methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diacetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(2-hydroxy-5-piperidin-1-yl-phenoxy)-phenyl]-amide acetate;
4-(3-piperidin-1-yl-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-morpholin-4-yl-phenyl)-amide diformate;
N-{2-methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-benzamide;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4-phenoxy-phenyl)-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-dimethylamino-phenoxy)-phenyl]-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-trifluoromethoxy-phenoxy)-phenyl]-amide acetate;
6-phenoxy-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[3-(3,3-dimethyl-piperidin-1-yl)-phenoxy]-phenyl}-amide;
6-(3-piperidin-1-yl-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole triacetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-isopropoxy-phenoxy)-phenyl]-amide acetate;
4-(4-morpholin-4-ylmethyl-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;
4-{4-[4-(4-methyl-piperazin-1-ylmethyl)-benzoyl]-benzoylamino}-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester;
4-[4-(4-methyl-piperazin-1ylmethyl)-benzoyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(3-methoxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(2-methoxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(2-hydroxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-benzamide;

4-(3-morpholin-4-ylmethyl-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-[3-(4-methyl-piperazin-1-ylmethyl)-benzoyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-4-chloro-benzamide;

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-3-chloro-benzamide;

N-{3-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-4-phenoxy-benzamide;

N-{3-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-4-benzene sulphonyl-benzamide;

N-[3-amino-1-(4-chloro-phenyl)-propyl]-3-(1H-pyrazol-4-yl)-benzamide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-cyclopentyloxy-phenoxy)-phenyl]-amide formate;

N-[{-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-benzoyl-benzamide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3-methyl-3H-imidazol-4-ylethynyl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-thiophen-3-ylethynyl-phenyl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4-methyl-piperazin-1-yl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4,4-dimethyl-piperidin-1-yl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methyl-biphenyl-3-yl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methoxy-biphenyl-3-yl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-cyano-biphenyl-3-yl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[5-(3,3-dimethyl-piperidin-1-yl)-2-hydroxy-phenoxy]-phenyl}-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[5-(4,4-dimethyl-piperidin-1-yl)-2-hydroxy-phenoxy]-phenyl}-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methoxy-biphenyl-3-yl)-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3'-methyl-biphenyl-4-yl)-amide;

cyclohexanecarboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate;

4'-trifluoromethyl-biphenyl-3-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(1H-pyrazol-4-yl)-phenyl]-amide;

2-amino-N-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide acetate;

2-amino-N-(4'-methoxy-biphenyl-3-yl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide acetate;

1-benzoyl-piperidine-4-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-pyrimidin-2-yl-phenyl)-amide diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-amide diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-pyridin-3-yl-phenyl)-amide diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-tert-butyl-phenyl)-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-benzooxazol-2-yl-phenyl)-amide diacetate;

2-amino-N-(3-tert-butyl-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride;

2-amino-N-(3-isopropoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(5-fluoro-pyrimidin-2-yl)-phenyl]-amide diacetate;

2-amino-N-(3-benzooxazol-2-yl-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride;

2-amino-N-[3-(3,3-dimethyl-but-1-ynyl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;

2-amino-N-[3-(3,3-dimethyl-but-1-ynyl)-phenyl]-2-[4-(5-ethyl-1H-pyrazol-4-yl)-phenyl]-acetamide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-oxazol-5-yl-phenyl)-amide diacetate;

4-(5-phenyl-1H-imidazol-2-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-cyclopentyloxy-phenoxy)-phenyl]-amide formate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(2-methyl-pyrimidin-4-yl)-phenyl]-amide trihydrochloride;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(6-methyl-pyridazin-3-yl)-phenyl]-amide acetate;

4-[4-(3-methyl-1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide acetate;

4-[4-(3-ethyl-1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-piperidin-1-yl-phenyl)-amide hydrochloride;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid methyl-(3-piperidin-1-yl-phenyl)-amide hydrochloride;

2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzooxazole hydrochloride;

4'-methoxy-biphenyl-3-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide, hydrochloride salt;

6-(4-methoxy-phenyl)-pyridine-2-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide, hydrochloride salt;

3-(5-methyl-tetrazol-1-yl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;
4-(4-chloro-phenyl)-piperidine-4-carboxylic acid [3-(1H-pyrazol-4-yl)-phenyl]-amide;
2-amino-2-(4-chloro-phenyl)-N-[3-(1H-pyrazol-4-yl)-phenyl]-acetamide;
3-[(Z)-3,3-dimethyl-1-(1H-pyrazol-4-yl)-but-1-enyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;
N-(3-benzooxazol-2-yl-phenyl)-2-piperazin-1-yl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate;
2-amino-N-[3-(5-methyl-thiazol-2-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate;
2-amino-N-[3-(4-methyl-pyridin-2-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate;
1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(5-fluoro-pyrimidin-2-yl)-phenyl]-amide;
4-[3-(5-fluoro-pyrimidin-2-yl)-phenylcarbamoyl]-1,1-dimethyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidinium;
2-amino-N-[3-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;
C-(1H-benzoimidazol-2-yl)-C-[4-(1H-pyrazol-4-yl)-phenyl]-methylamine;
4-(5-phenyl-oxazol-2-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
4-(4-phenyl-imidazol-1-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
C-(5-phenyl-1H-imidazol-2-yl)-C-[4-(1H-pyrazol-4-yl)-phenyl]-methylamine;
and salts, solvates, tautomers and N-oxides thereof.

Salts, Solvates, Tautomers, Isomers, N-Oxides, Esters, Prodrugs and Isotopes

In this section, as in all other sections of this application, unless the context indicates otherwise, references to formula (I) include formulae (I^0) and (Ia) and references to all sub-groups, preferences and examples thereof as defined herein.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms thereof, for example, as discussed below.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and

references to compounds of the formula (I) include the salt forms of the compounds. As in the preceding sections of this application, all references to formula (I) should be taken to refer also sub-groups thereof unless the context indicates otherwise.

Salt forms may be selected and prepared according to methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. For example, acid addition salts may be prepared by dissolving the free base in an organic solvent in which a given salt form is insoluble or poorly soluble and then adding the required acid in an appropriate solvent so that the salt precipitates out of solution.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1*S*)-camphor-10-sulphonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and (±)-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic, (±)-DL-mandelic, methanesulphonic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, toluenesulphonic (e.g. *p*-toluenesulphonic), undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

One particular group of acid addition salts includes salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

Another group of acid addition salts includes salts formed from acetic, adipic, ascorbic, aspartic, citric, DL-Lactic, fumaric, gluconic, glucuronic, hippuric, hydrochloric, glutamic, DL-malic, methanesulphonic, sebacic, stearic, succinic and tartaric acids.

The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed. In stronger acids, the basic pyrazole nitrogen, as well as the nitrogen atom in the group NR^2R^3, may take part in salt formation. For example, where the acid has a pKa of less than about 3 (e.g. an acid such as hydrochloric acid, sulphuric acid or trifluoroacetic acid), the compounds of the invention will typically form salts with 2 molar equivalents of the acid.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

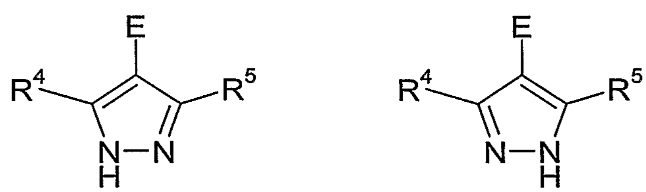
Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

Compounds of the formula (I) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

For example, in compounds of the formula (I) the pyrazole group may take either of the following two tautomeric forms A and B.



A B

For simplicity, the general formula (I) illustrates form A but the formula is to be taken as embracing both form A and form B.

Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers and diastereoisomers), either as individual optical isomers, or mixtures or two or more optical isomers, unless the context requires otherwise.

For example, the group A can include one or more chiral centres. Thus, when L^3 (or E) and L^1 are both attached to the same carbon atom on the linker group A, the said carbon atom is typically chiral and hence the compound of the formula (I) will exist as a pair of enantiomers (or more than one pair of enantiomers where more than one chiral centre is present in the compound).

The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers) or they may be characterised in terms of their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 385-415.

Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid, (-)-di-toluloyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). In one embodiment of the invention, formula (I) includes within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. In another embodiment of the invention, formula (I) does not include within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. Examples of esters are compounds containing the group -C(=O)OR, wherein R is an ester

substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, -C(=O)OCH$_3$, -C(=O)OCH$_2$CH$_3$, -C(=O)OC(CH$_3$)$_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, -OC(=O)CH$_3$ (acetoxy), -OC(=O)CH$_2$CH$_3$, -OC(=O)C(CH$_3$)$_3$, -OC(=O)Ph, and -OC(=O)CH$_2$Ph.

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:
C_{1-7}alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
C_{1-7} aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and
acyloxy-C_{1-7}alkyl (e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)-carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)-carbonyloxyethyl).

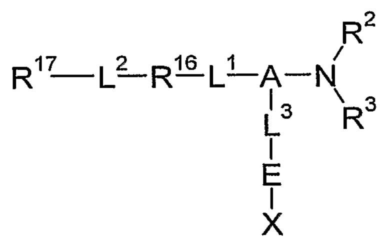
Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for

example, as in antigen-directed enzyme pro-drug therapy (ADEPT), gene-directed enzyme pro-drug therapy (GDEPT) and ligand-directed enzyme pro-drug therapy (LIDEPT). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

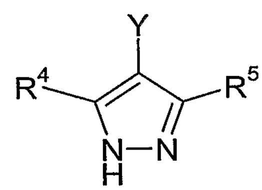
Methods for the preparation of compounds of the formula (I)

In this section, as in all other sections of this application, unless the context indicates otherwise, references to formula (I) include formula (Ia) and references to all sub-groups, preferences and examples thereof as defined herein.

Compounds of the formula (I) can be prepared by reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:



(X)



(XI)

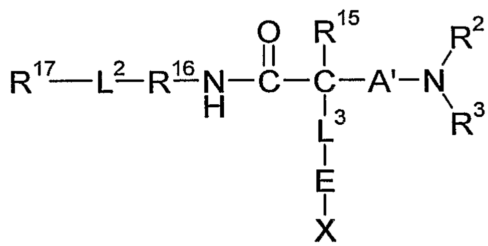
wherein E, L^1, L^2, L^3, R^1 to R^5 , R^{16} and R^{17} are as hereinbefore defined, one of the groups X and Y is chlorine, bromine or iodine or a trifluoromethanesulphonate (triflate) group, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue.

The reaction can be carried out under typical Suzuki Coupling conditions in the presence of a palladium catalyst such as bis(tri-*t*-butylphosphine)palladium and a base (e.g. a carbonate such as potassium carbonate). The reaction may be carried out in an aqueous solvent system, for example aqueous ethanol, and the reaction mixture is typically subjected to heating, for example to a temperature in excess of 100°C.

In these preparative procedures, the coupling of the aryl or heteroaryl group E to the pyrazole is accomplished by reacting a halo-pyrazole or halo-aryl or heteroaryl compound with a boronate ester or boronic acid in the presence of a palladium catalyst and base. Many boronates suitable for use in preparing compounds of the invention are commercially available, for example from Boron Molecular Limited of Noble Park, Australia, or from

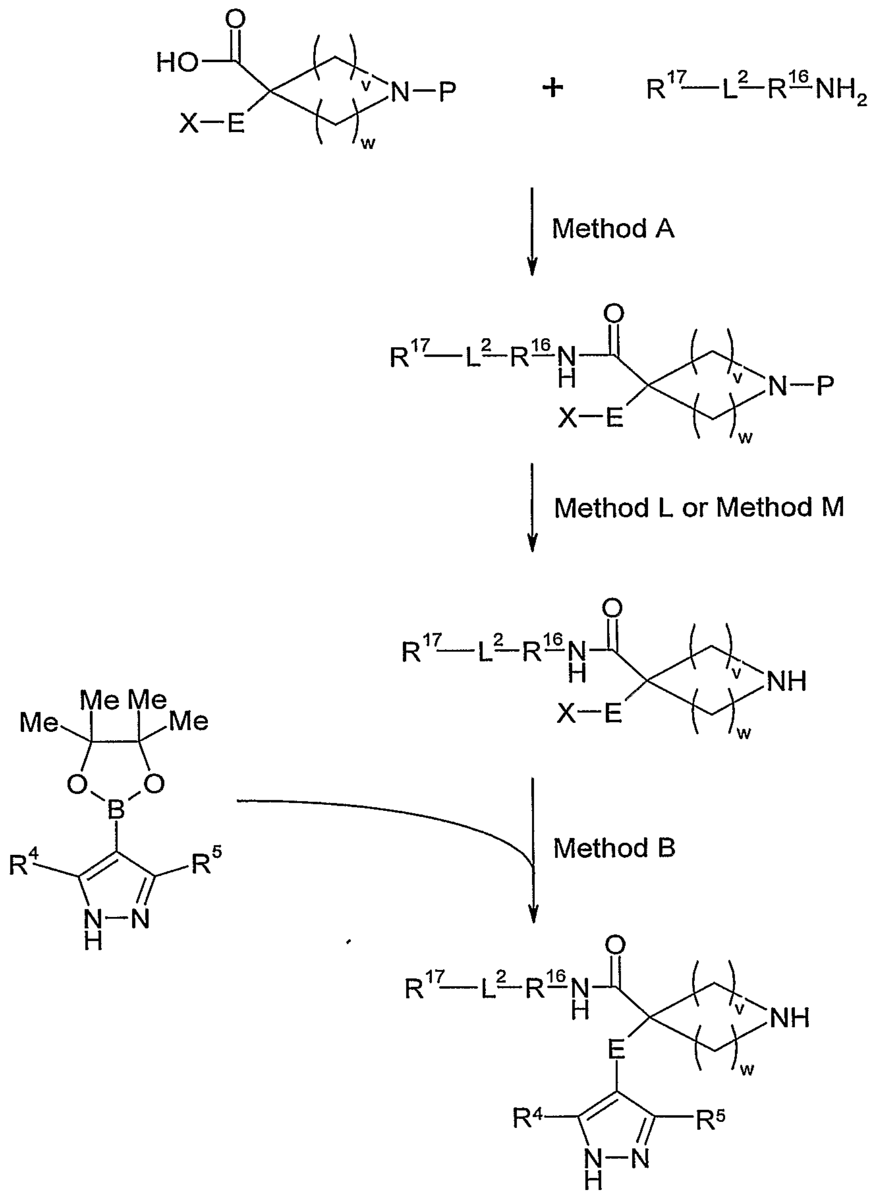
Combi-Blocks Inc, of San Diego, USA. Where the boronates are not commercially available, they can be prepared by methods known in the art, for example as described in the review article by N. Miyaura and A. Suzuki, *Chem. Rev.* 1995, *95*, 2457. Thus, boronates can be prepared by reacting the corresponding bromo-compound with an alkyl lithium such as butyl lithium and then reacting with a borate ester. The resulting boronate ester derivative can, if desired, be hydrolysed to give the corresponding boronic acid.

The route to a compound of formula (I) *via* a compound of formula (Xa) is set out in Scheme 1.



(Xa)

wherein R^2, R^3, R^{15}, R^{16}, R^{17}, A', E and X are as defined above, L^3 is a bond and the linker L^1 is represented by NHC(O); or protected versions thereof.



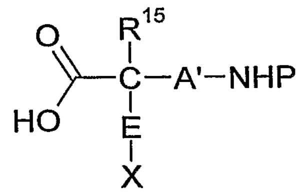
Scheme 1

A compound of formula (Xa) may be prepared by reacting a compound of formula (XX):

$$R^{17}\text{-}L^{2}\text{-}R^{16}\text{-}NH_2 \qquad \text{(XX)}$$

where R^{17}, R^{16} and L^{2} are as defined above;

with a protected compound of formula (XXIa):

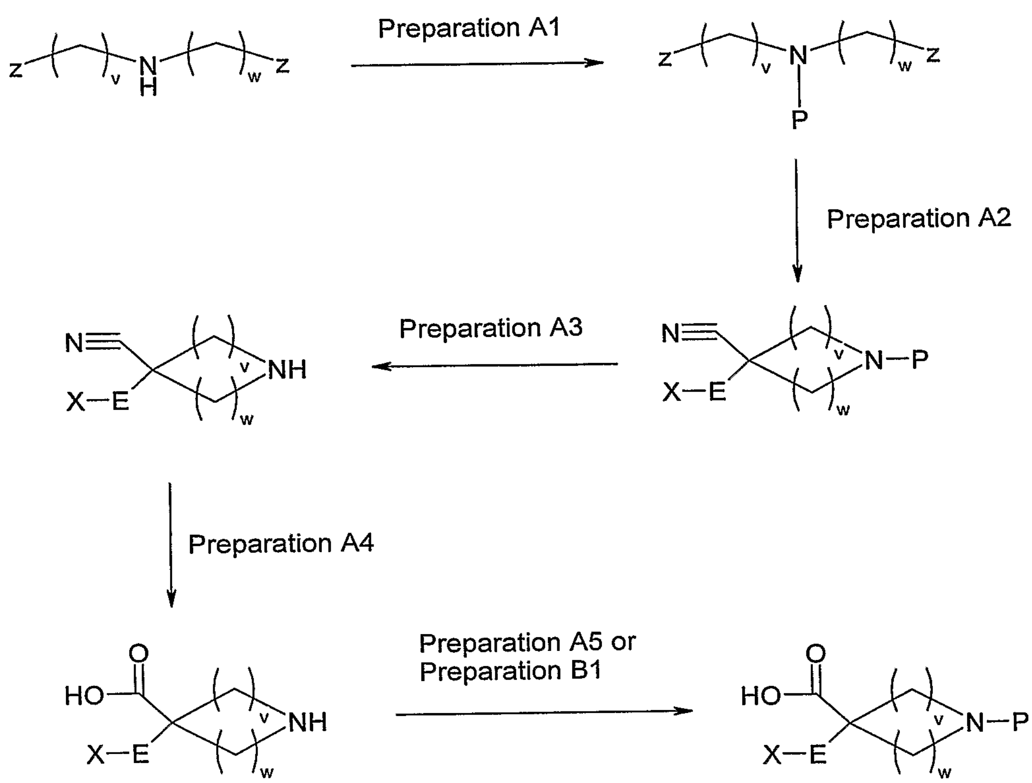


(XXIa)

where R^{15}, A', E and X are as defined above and P is a suitable protecting group for amines, for example a C(O)O(C_1-C_6 alkyl) or C(O)O-benzyl group.

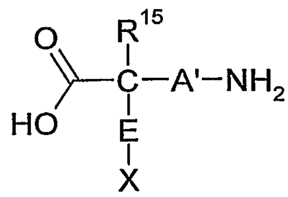
The reaction may be carried out by any suitable amide coupling method, for example, any of methods A1 to A3 as set out in the Examples below.

The preparation of compounds of formula (XXIa) is illustrated below in Scheme 2.



Scheme 2

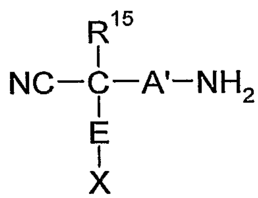
As is shown in Scheme 2, compounds of formula (XXIa) may be prepared by protecting an amine of formula (XXI):



(XXI)

by any suitable method, for example by reaction with fluorenylmethyl succinimidyl carbonate.

Compounds of formula (XXI) may be prepared from compounds of formula (XXII):

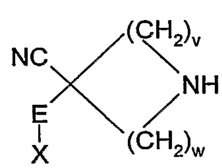


(XXII)

wherein R^{15}, A', E and X are as defined above by heating the nitrile in an aqueous acid, for example hydrochloric acid. Typically, the reaction is carried out by dissolving the nitrile in the aqueous acid and heating under reflux for several hours or even days. Additional concentrated acid may be added during the process if required.

The nitriles of formula (XXII) may be prepared by known methods when the linker A' is a hydrocarbon chain.

However, compounds of formula (XXIIa) cannot be prepared in this way:



(XXIIa)

wherein X and E are as defined above and v and w are each 1 to 3, provided that they cannot both be 3; and
wherein any of the CH_2 groups can be replaced by O, S or NH.

Compounds of formula (XXIIa) may be prepared from compounds of formula (XXIIIa):

$Z\text{-}(CH_2)_v\text{-}N(P)\text{-}(CH_2)_w\text{-}Z$ (XXIIIa)

where v and w are as defined above, Z is a leaving group, particularly a halogen such as Cl or Br and P is an amine protecting group, for example a carbamate, particularly a C_1-C_6 alkyl or benzyl carbamate;
by a cyclisation method which is described in WO-A-2004022539.

The protected compound of formula (XXIIIa) may be prepared from the unprotected secondary amine of formula (XXIII):

$$Z\text{-}(CH_2)_v\text{-}NH\text{-}(CH_2)_w\text{-}Z \qquad \text{(XXIII)}$$

wherein v, w and Z are as defined above;
by the method described in *J. Chem. Soc., Perkin Trans. 1*, 2000, 3444-3450.

Compounds of formula (XXIII) are readily available or may be prepared by methods known to those skilled in the art.

Compounds of formula (XX) as defined above may be prepared in a number of ways depending on the nature of the R^{16}, R^{17} and L^2 groups.

For example, when L^2 is a bond and R^{17} is an aryl or heteroaryl group, the compound of formula (XX) can be prepared by reacting an amine of the formula Hal-R^{16}-NH_2 , where Hal is a halogen atom, with a compound R^{17}-Bor, where Bor is a boronate group, under Suzuki coupling conditions, for example as described elsewhere herein.

Another method of preparing the compound of formula (XX) is by the reduction of a compound of formula (XXIV):

$$R^{17}\text{-}L^2\text{-}R^{16}\text{-}NO_2 \qquad \text{(XXIV)}$$

where R^{16} and R^{17} and L^2 are as defined above;
for example using hydrogenation over a palladium/carbon catalyst as described in the Examples in Method E and as illustrated in Scheme 3.

<u>Scheme 3</u>

$$R^{17}\text{—}L^2\text{—}R^{16}\text{—}NO_2 \xrightarrow{\text{Method E}} R^{17}\text{—}L^2\text{—}R^{16}\text{—}NH_2$$

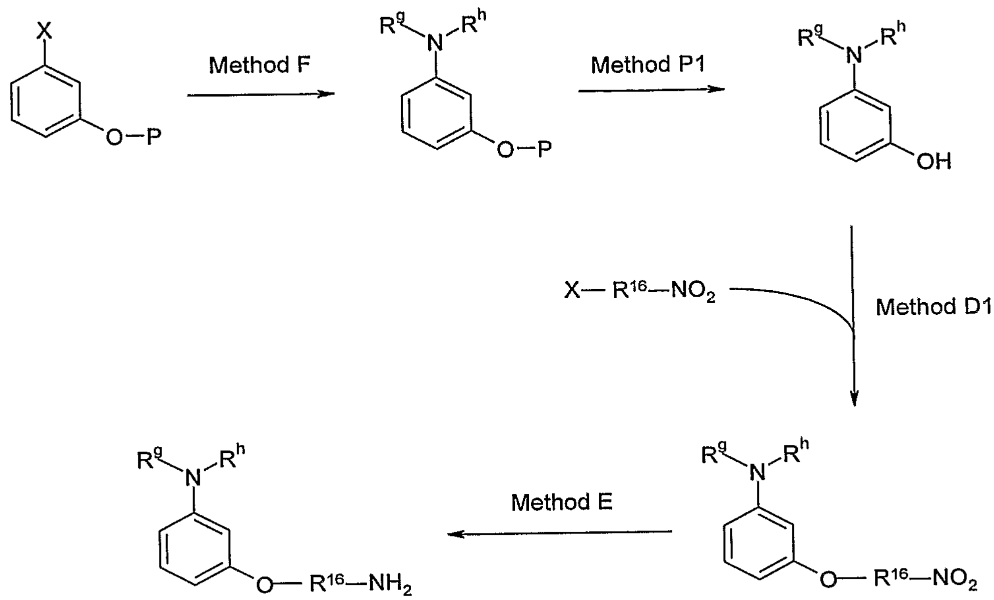
The method of obtaining the compound of formula (XXIV) depends largely upon the nature of R^{16}, R^{17} and L^2. For example, compounds in which R^17 and L^2 are absent are, in general, readily available or may be prepared by methods known to those of skill in the art.

When the linker L^2 is SO_2, many of the compounds of formula (XXIV) are also readily available or can be prepared by methods well known to those skilled in the art. For example, one suitable starting material for these compounds is benzene sulphonyl benzoic acid. Equivalent acids with other sulphonyl substituents can be prepared by known methods. This also applies to compounds when the linker is SO.

Compounds in which the linkers are alkylene, alkenylene or alkynylene groups can also be prepared by known methods, for example by using nucleophilic substitution reactions or, for alkynylene linkers, the Sonogashira cross-coupling reaction described in Procedure C1 of the Examples below.

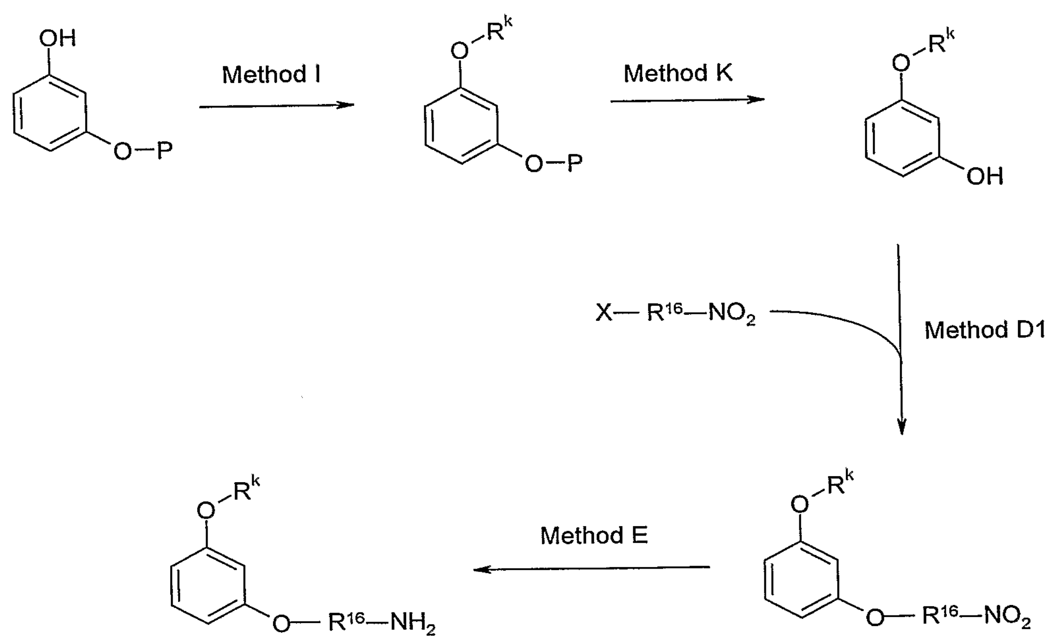
Compounds of formula (XXIV) in which L^2 is -O- may, for example be prepared by one of the methods set out in Scheme 4 or Scheme 5.

Scheme 4 illustrates the preparation of nitro compounds where L^2 is oxygen and R^{17} is phenyl mono-substituted with a nitrogen-containing group. In Scheme 4, R^g and R^h are each hydrogen, C_{1-6} alkyl or NR^gR^h forms a five or six membered heterocyclic ring optionally containing another heteroatom ring member selected from O and N, examples of such heterocyclic rings being morpholine, piperidine and N-methylpiperazine.



Scheme 4

Scheme 5 illustrates the preparation of nitro compounds where L_2 is oxygen, R^{17} is phenyl and mono-substituted with a oxygen-containing group. In Scheme 5, R^k is typically an alkyl group.



Scheme 5

Schemes 4 and 5 show the routes used when R^{17} is a mono-substituted aryl group. A skilled chemist would be able to devise a similar route for the preparation of a compound of formula (XX) in which R^{17} is a di-substituted or tri-substituted aryl group.

In the methods of Schemes 4 and 5, a compound of formula (XXV):

R^{17}-OH (XXV)

wherein R^{17} is as defined above;

is reacted with a compound of formula (XXVI):

X-R^{16}-NO_2 (XXVI)

where R^{16} is as defined above and X is a leaving group, typically a halogen such as F. Examples of reaction conditions which may be used are described in the Examples below in Method D. An equivalent reaction may be used for compounds in which the linker L^2 is -S-.

When the linker L^2 is a CONH or NHCO group, the compound of formula (XXIV) may be prepared using an amide coupling reaction of compounds of formulae (XXVII) and (XXVIII):

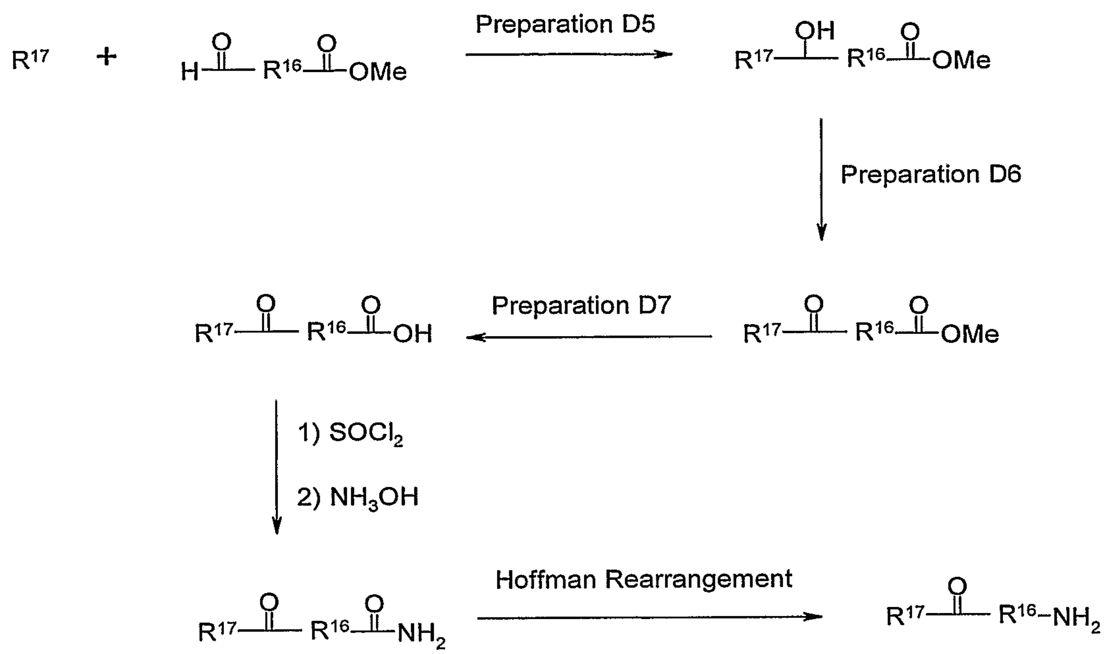
R^{17}-NH_2	HOOC-R^{16}-NO_2
(XXVII)	(XXVIII)

or (XIX) and (XXX):

R^{17}-COOH	H_2N-R^{16}-NO_2
(XXIX)	(XXX)

The reaction conditions which may be used are described in the Examples below in Method A.

When the linker L^2 is -C(O)-, the route for preparing compounds of formula (XX) as defined above is shown in Scheme 6 below.



Scheme 6

The compound of formula (XX) may be prepared from a compound of formula (XXXI):

R^{17}-C(O)-R^{16}-C(O)NH_2 (XXXI)

wherein R^{16} and R^{17} are as defined above;
by a Hoffman rearrangement reaction using standard conditions.

An amide of formula (XXXI) may be prepared from the equivalent carboxylic acid of formula (XXXII):

R^{17}-C(O)-R^{16}-C(O)OH (XXXIIa)

wherein R^{16} and R^{17} are as defined above;
by treatment with sulphonyl chloride and aqueous ammonia.

Compounds of formula (XXXII) may be prepared from esters of formula (XXXIII):

R^{17}-C(O)-R^{16}-C(O)R^{20} (XXXIII)

wherein R^{16} and R^{17} are as defined above and R^{20} is C_{1-6} alkoxy;
using, for example, alkaline hydrolysis as described in Preparation D7 in the Examples below. In Scheme 6, R^{20} is methoxy but any suitable alkyl ester can be used.

Compounds of formula (XXXIII) may be prepared from compounds of formula (XXXIV):

R^{17}-CH(OH)-R^{16}C(O)R^{20} (XXXIV)

wherein R^{16} R^{17} and R^{20} are as defined above;
by an oxidation process, for example as described in Preparation D6 in the Examples.

Compounds of formula (XXXIV) may be prepared by reacting a compound of formula (XXXV):

HC(O)-R^{16}-C(O)R^{20} (XXXV)

wherein R^{16} R^{17} and R^{20} are as defined above;

with a compound of formula (XXXVI):

R^{17}-H (XXXVI)

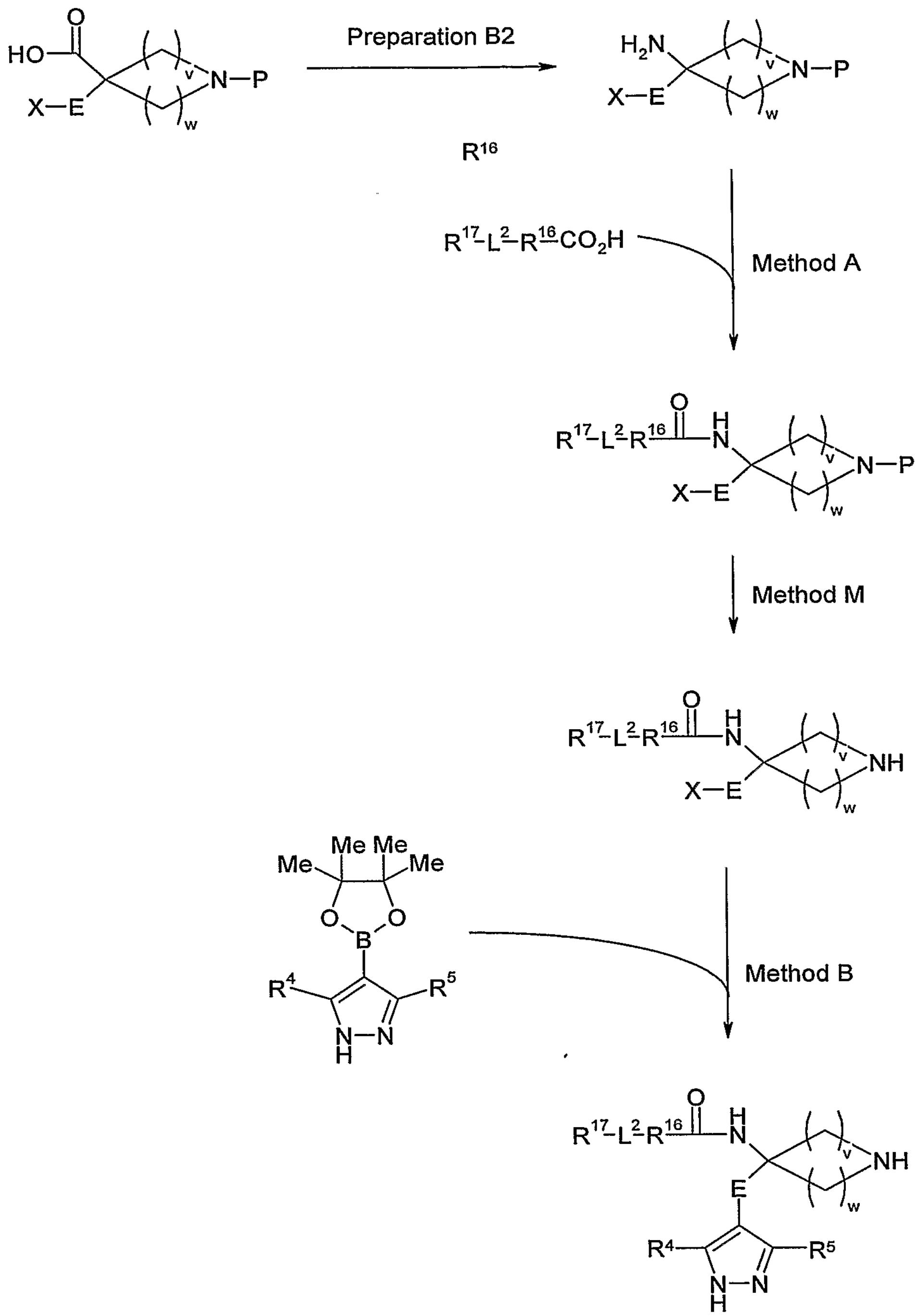
where R^{17} is as defined above.
Examples of suitable reaction conditions are set out in Preparation D5 in the Examples below.

An equivalent method can be used for the preparation of a compound of formula (XX) when the linker L^2 is -C(S)-.

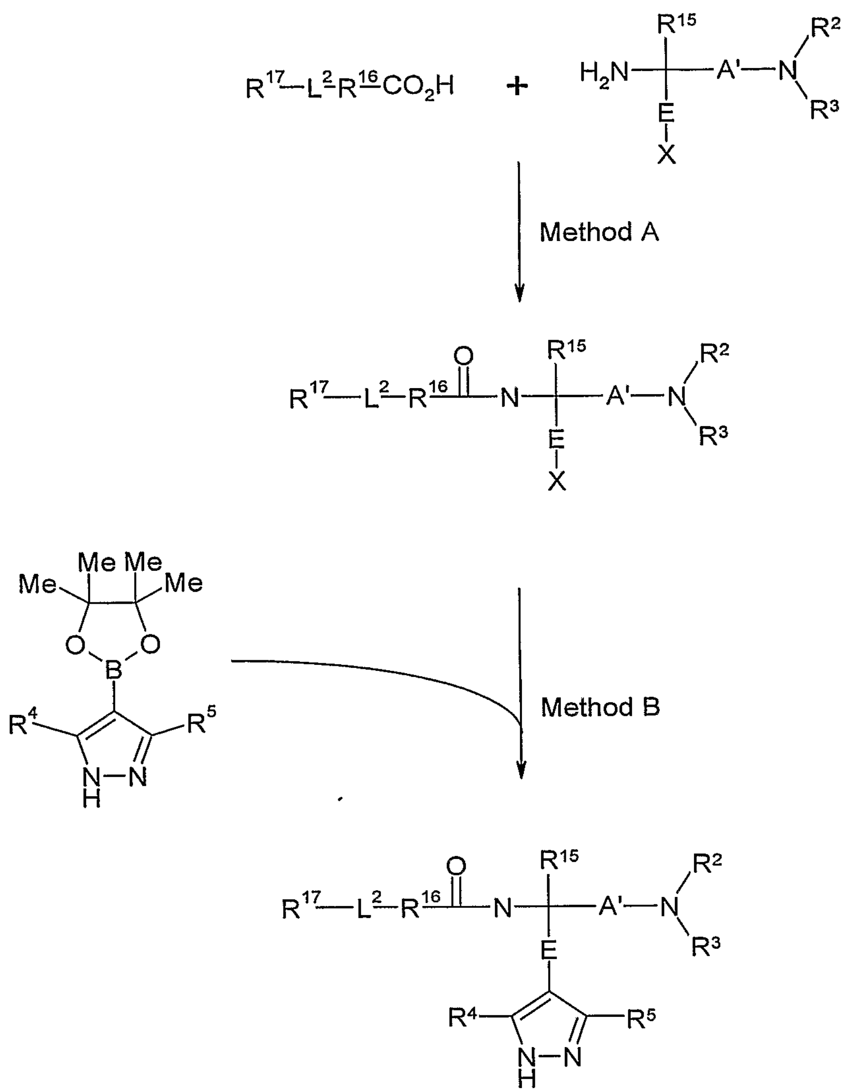
Schemes 7 and 8 illustrate the preparation of a compound of formula (I) *via* a compound of formula (Xb):

$$(R^{17})_p(L^2)_n\text{-}R^{16}\text{-C(O)NH-}\underset{\underset{\textstyle \text{E-X}}{|}}{\overset{\overset{\textstyle R^{15}}{|}}{\text{C}}}\text{-A'-NR}^2\text{R}^3 \qquad \text{(Xb)}$$

in which R^2, R^3, R^{15}, R^{16}, R^{17}, A', E, X, p and n are as defined above and the linker L^1 is represented by NHC(O); or protected versions thereof.



Scheme 7



Scheme 8

As illustrated in Schemes 7 and 8, the compound of formula (Xb) may be prepared by reacting a compound of formula (XXXII):

$$R^{17}\text{-}L^{2}\text{-}R^{16}\text{-COOH} \qquad \text{(XXXII)}$$

where R^{17}, R^{16} and L^2 are as defined above;

with a protected compound of formula (XXXVIIa):

$$\begin{array}{c} R^{15} \\ | \\ H_2N\text{-C-A'-NHP} \\ | \\ \text{E-X} \end{array} \qquad \text{(XXXVIIa)}$$

where R^{15}, A', E and X are as defined above and P is a suitable protecting group for amines, for example a C(O)O(C_1-C_6 alkyl) or C(O)O-benzyl group.

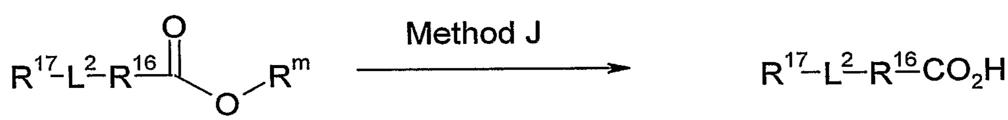
The reaction may be carried out by any suitable amide coupling method, for example, any of methods A1 to A3 as set out in the Examples below.

Compounds of formula (XXXVIIa) may be prepared from compounds of formula (XXIa) above by reacting with triethylamine and sodium azide as set out in Preparation B of the Examples below, and as shown in Scheme 7.

Many compounds of formula (XXXIIa) or their methyl or ethyl esters are readily available or can be prepared by methods familiar to those of skill in the art, for example using the hydrolysis method shown in Scheme 9. Examples of such compounds are 4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzoyl]-benzoic acid ethyl ester and 4-(4-Morpholin-4-ylmethyl-benzoyl)-benzoic acid ethyl ester.

In Scheme 9, R^m can be a C_{1-6} alkyl group as defined for R^{20} above.

Scheme 9

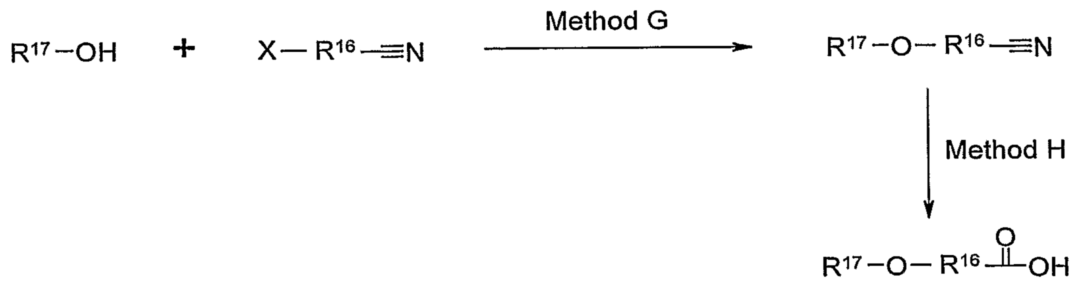


Other compounds of formula (XXXIIa) may be prepared as shown in Scheme 10 by the alkaline hydrolysis of nitriles of formula (XXXVII):

$$R^{17}\text{-}L^2\text{-}R^{16}\text{-}C{\equiv}N \qquad \text{(XXXVII)}$$

where R^{17}, R^{16} and L^2 are as defined above.

Scheme 10



A procedure for carrying out this reaction is described in Method H of the Examples below.

Compounds of formula (XXXVII) may be prepared by methods analagous to those described for the preparation of compound (XXIV) above but using compounds in which the R^{16} moiety is linked to a nitrile rather than a nitro group.

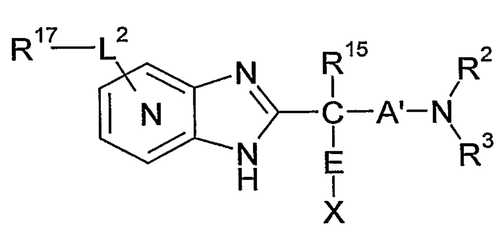
In compounds where the linker L^2 is -O-, nitriles of formula (XXXVII) may also be prepared from compounds of formulae (XXXVIII) and (XXXIX):

$R^{17}OH$	$X\text{-}R^{16}\text{-}C\equiv N$
(XXXVIII)	(XXXIX)

where R^{16} and R^{17} are as described above and X is a leaving group, especially a halogen such as F, Cl or Br.

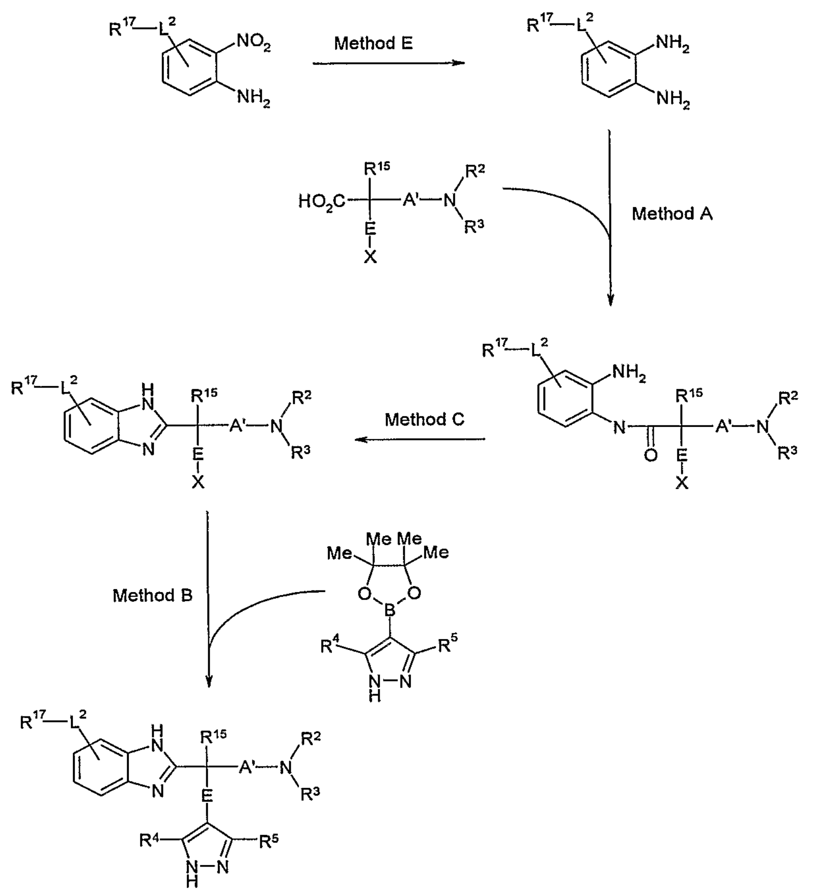
The reaction is carried under mildly alkaline conditions and is described in Method G of the Examples below.

A route to compounds of formula (I) *via* compounds of formula (Xc) is illustrated below in Scheme 11.



(Xc)

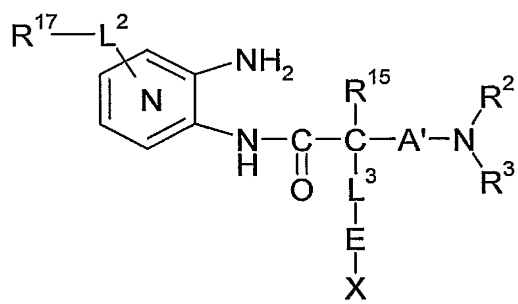
in which R^2, R^3, R^{15}, R^{17}, A', E, L^2, L^3 and X are as defined above. The "N" shown in the six membered ring indicates that the ring can be carbocyclic (e.g. as in a benzimidazole) or can contain one or two nitrogen atoms. In Scheme 11, the process illustrated gives rise to benzimidazoles but it will be appreciated that the route shown in Scheme 11 may be adapted used to prepare aza-analogues of benzimidazoles. Also, in the compounds of Scheme 11, the linker L^3 is absent and hence E is attached directly to A. However, the methods described in Scheme 11 may also be applied to compounds wherein a linker group L^3 is present.



Scheme 11

The method shown in Scheme 11 is a standard method for the preparation of benzimidazoles. When the combination of R^{16} and L^2 is another aromatic fused bicyclic ring system, the compounds can be prepared using known standard methods. For example, methods for the synthesis are known to those of skill in the art.

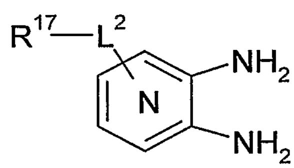
As shown in Scheme 11, the compounds of formula (Xc) may be prepared from compounds of formula (XL):



(XL)

in which R^2, R^3, R^{15}, R^{17}, A', E, and X are as defined above, and the ring "N" may be a carbocyclic or nitrogen-containing ring; using the methodology described in Method C of the Examples.

Compounds of formula (XL) in may be prepared by reacting a protected compound of formula (XXIa) as defined above with a compound of formula (XLI):

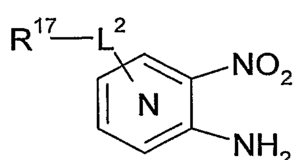


(XLI)

wherein R^{17} are as defined above;

Any suitable amide coupling reaction can be used and a number of such reactions are set out in Method A of the Examples below.

Compounds of formula (XLI) may be prepared by reducing compounds of formula (XLII):

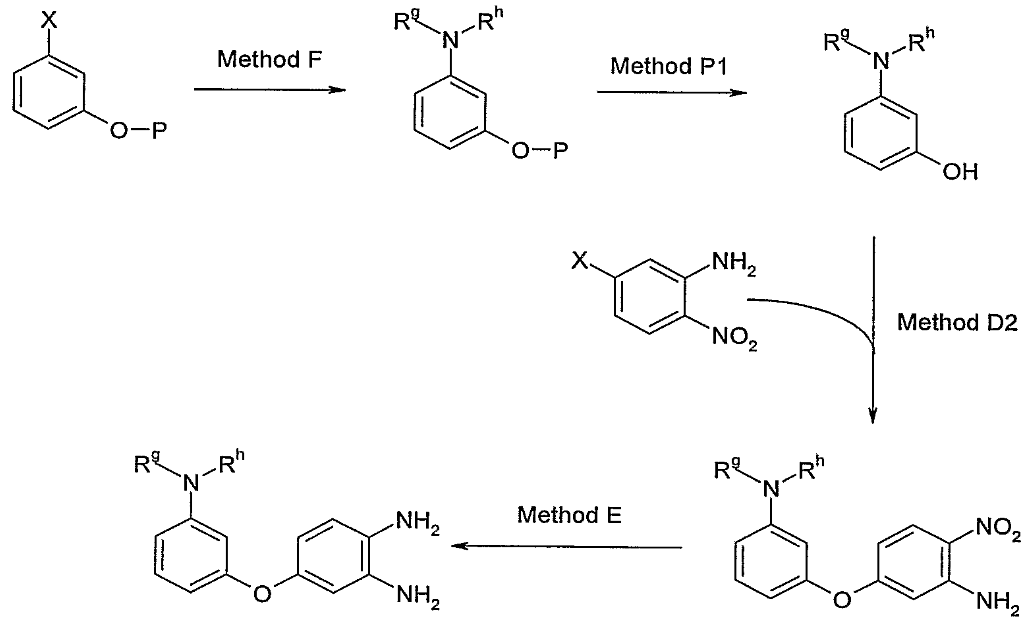


(XLII)

wherein R^{17} is as defined above;
for example by hydrogenation using a palladium catalyst as set out in Method E of the Examples.

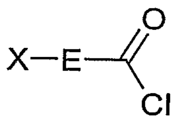
Compounds of formula (XLII) are commercially available or may be prepared using methods which are analogous to the methods used for the preparation of compound of formula (XXIV), for example as shown in Scheme 12.

Scheme 12

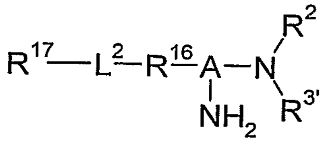


In Scheme 12, R^g and R^h are each hydrogen, C_{1-6} alkyl or NR^gR^h forms a five or six membered heterocyclic ring optionally containing another heteroatom ring member selected from O and N, examples of such heterocyclic rings being morpholine, piperidine and N-methylpiperazine.

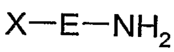
Compounds of formula (X) in which L^3 is a NHCO or CONH group directly linked to E and in which L^1 is a bond may be prepared from compounds of formula (XLIII) and (XLIV) or (XLV) and (XLVI)



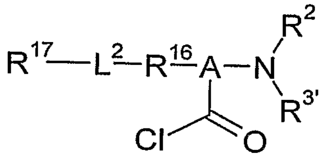
(XLIII)



(XLIV)



(XLV)



(XLVI)

where X, E, A, L^2, R^{16} and R^{17} are as defined above and $R^{3'}$ is a suitable amine protecting group. Alternatively, for the preparation of compounds wherein R^2 and R^3 are both other than hydrogen, the amine protecting group may be omitted.

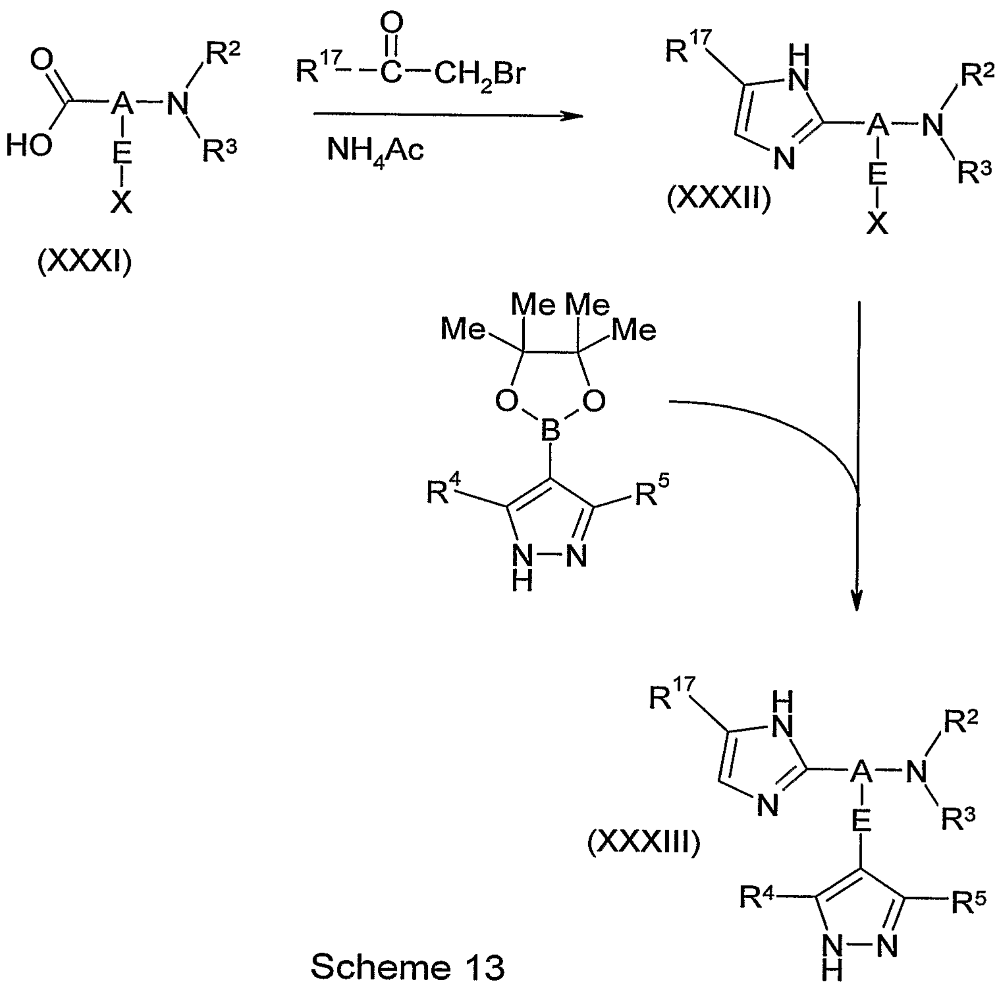
This reaction to form the amide bond is described in method A1 of the Examples below.

As an alternative to forming the amide bond using an acid chloride, the carboxylic acid may be reacted with the amine in the presence of an amide coupling reagent such as a reagent of the type commonly used in the formation of peptide linkages. Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan *et al*, *J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (referred to herein either as EDC or EDAC) (Sheehan *et al*, *J. Org. Chem., 1961, 26, 2525*), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and phosphonium-based coupling agents such as 1-benzo-triazolyloxytris-(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et al*, *Tetrahedron Letters*, 1990, 31, 205). Carbodiimide-based coupling agents are advantageously used in combination with 1-hydroxy-7-azabenzotriazole (HOAt) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115, 4397) or 1-hydroxybenzotriazole (HOBt) (Konig *et al*, *Chem. Ber.*, 103, 708, 2024-2034). Preferred coupling reagents include EDC (EDAC) and DCC in combination with HOAt or HOBt.

Methods for preparing compounds of formulae (XLIV) and (XLVI) are described in our earlier patent application PCT/GB04/005464.

Compounds of formulae (XLIII) and (XLV) may be prepared by methods known to those skilled in the art.

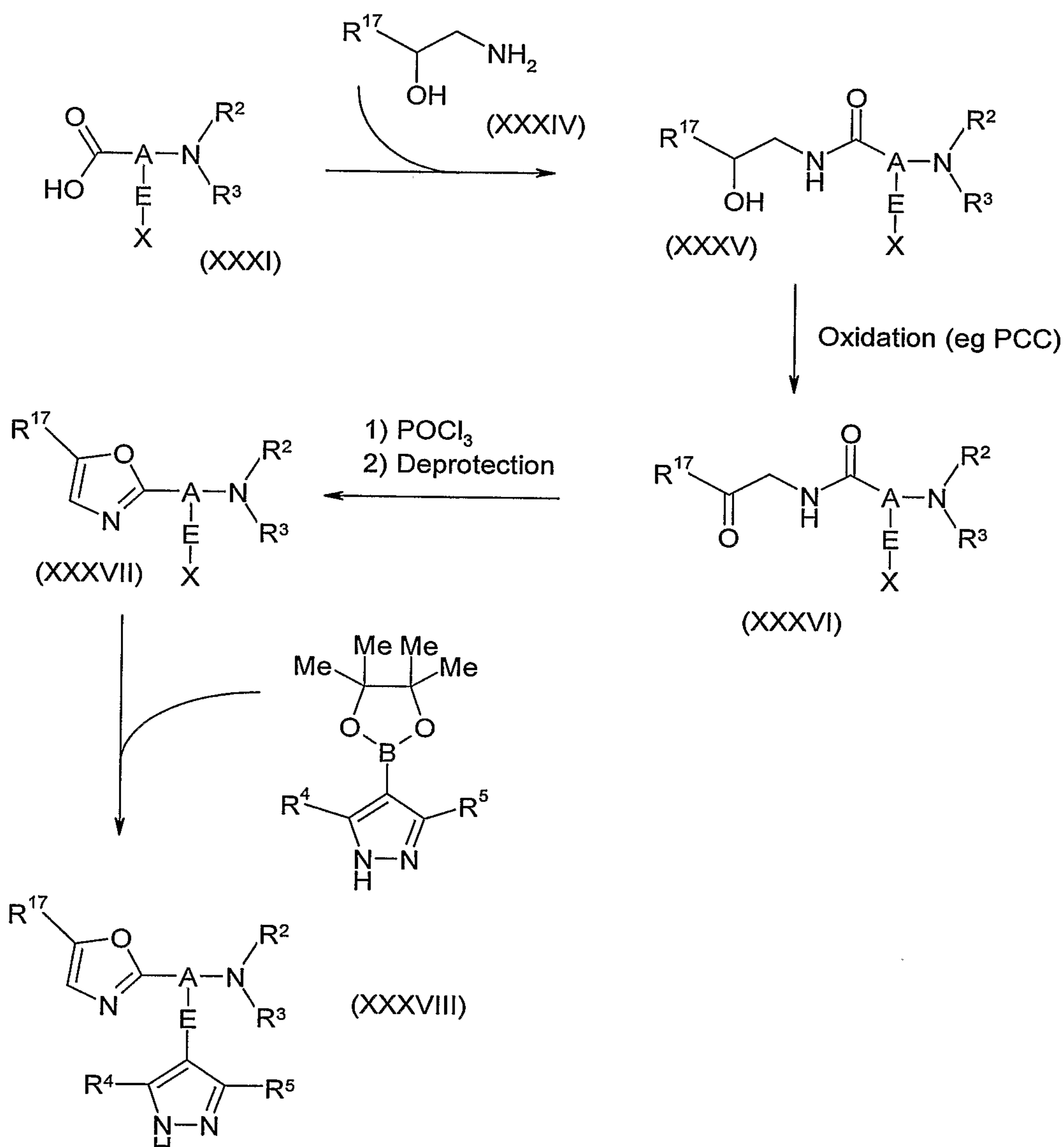
Compounds wherein R^{16} and L^1 together form an imidazole group, L^2 is a bond and R^{16} is an aryl or heteroaryl group can be prepared by the methods set out in Scheme 13.



Scheme 13

In Scheme 13, the amino-acid (XXXIII), in which the amino group is suitably protected (e.g. with an FMOC, boc or MOM protecting group), is reacted with an α-bromoketone R^{17}-C(O)CH_2Br and ammonium acetate according to the method described in US 2004/0077640 to give the imidazole compound (XXXII). The imidazole compound (XXXIII) is then reacted with a pyrazolyl boronate compound according under Suzuki coupling conditions as described above to give the product (XXXIII).

Compounds wherein R^{16} and L^1 together form an oxazole group, L^2 is a bond and R^{16} is an aryl or heteroaryl group can be prepared by the methods set out in Scheme 14.

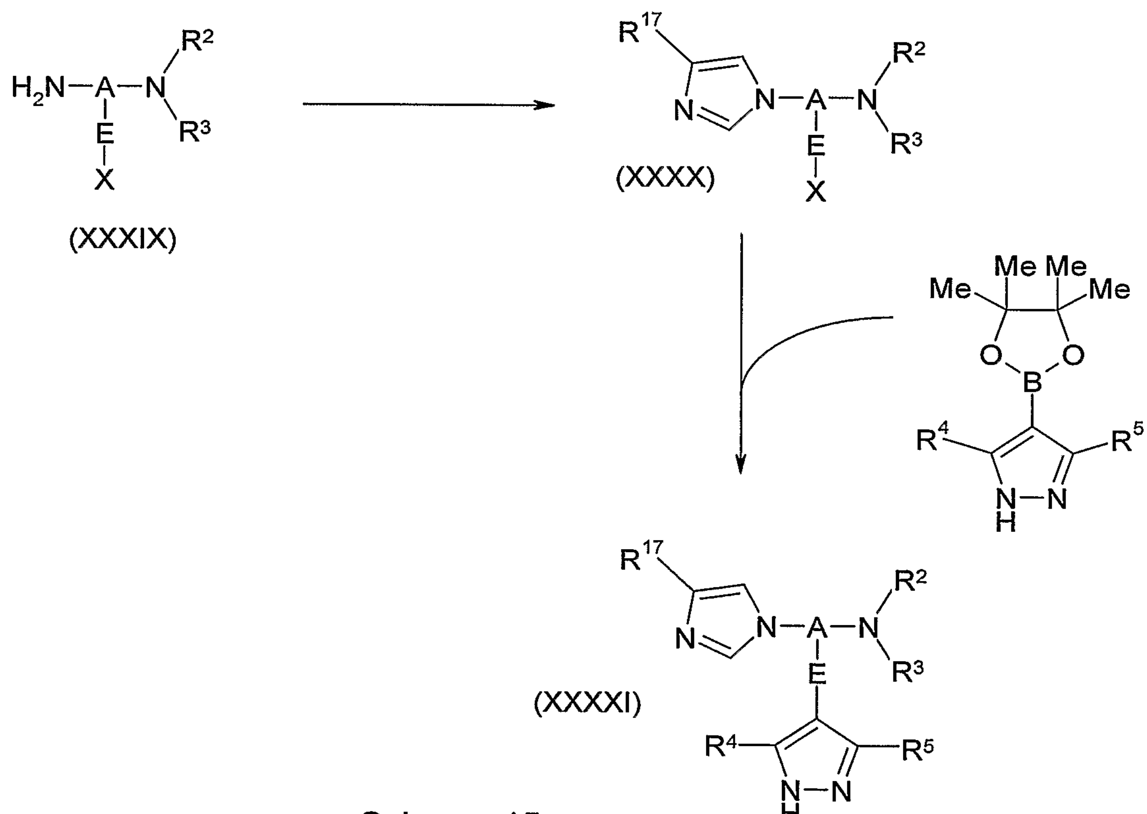


Scheme 14

In Scheme 14, the amino-acid (XXXI), in which the amino group NR^2R^3 is protected where necessary, is coupled with the hydroxy-amine (XXXIV) to form the amide (XXXV). The amide-forming step can be carried out by using the methods described above for the formation of amides. The hydroxy compound is then oxidised to the corresponding ketone

(XXXVI) using an oxidising agent such as pyridinium chlorochromate (PCC) and the ketone is subjected to a cyclisation dehydration reaction using a reagent such as phosphorus oxychloride to give the oxazole (XXXVIII). The oxazole is subjected to the Suzuki coupling procedures described above to give the compound. The amino-carboxylic acid starting materials for reaction Schemes 13 and 14 can be obtained commercially or prepared by methods well known to the skilled person or analogous thereto. Amino-acid compounds wherein E is a non-aromatic ring can be prepared by the methods described in Scheme 2 above.

Compounds of the formula (I) wherein R^{16} and L^1 together form an imidazole group which is linked to the moiety A through a nitrogen atom, L^2 is a bond and R^{16} is an aryl or heteroaryl group can be prepared by the methods set out in Scheme 15.



Scheme 15

In Scheme 15, the amino compound (XXXIX) can be cyclised to the imidazole using the procedure set out in Preparation M in the Examples section below. The imidazole

compound (XXXX) can then be coupled with the pyrazole boronate compound using the Suzuki coupling described above to give the compound (XXXXI).

Once formed, many compounds of the formula (I) can be converted into other compounds of the formula (I) using standard functional group interconversions. For example, compounds of the formula (I) in which the NR^2R^3 forms part of a nitrile group can be reduced to the corresponding amine. Compounds in which NR^2R^3 is an NH_2 group can be converted to the corresponding alkylamine by reductive alkylation, or to a cyclic group. Compounds wherein R^1 contains a halogen atom such as chlorine or bromine can be used to introduce an aryl or heteroaryl group substituent into the R^1 group by means of a Suzuki coupling reaction. Further examples of interconversions of one compound of the formula (I) to another compound of the formula (I) can be found in the examples below. Additional examples of functional group interconversions and reagents and conditions for carrying out such conversions can be found in, for example, *Advanced Organic Chemistry*, by Jerry March, 4th edition, 119, Wiley Interscience, New York, *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8).

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$,

-NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH_3)$_2$$C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), or as a 2-(phenylsulphonyl)ethyloxy amide (-NH-Psec). Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulphonyl (tosyl) and methanesulphonyl (mesyl) groups and benzyl groups such as a *para*-methoxybenzyl (PMB) group. A carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide. A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH_2NHC(=O)CH_3).

The 1(H) position of the pyrazole group in the compounds of the formula (I) or its precursors can be protected by a variety of groups, the protecting group being selected according to the nature of the reaction conditions to which the group is exposed. Examples of protecting groups for the pyrazole N-H include tetrahydropyranyl, benzyl and 4-methoxybenzyl groups.

Many of the chemical intermediates described above are novel and such novel intermediates form a further aspect of the invention.

Pharmaceutical Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Accordingly, in a further aspect, the invention provides compounds of the formula (I) and sub-groups thereof as defined herein in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, co-solvents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, *inter alia*, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended recipient. Pharmaceutical formulations for parenteral administration may also take the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents (R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230).

Liposomes are closed spherical vesicles composed of outer lipid bilayer membranes and an inner aqueous core and with an overall diameter of <100 μm. Depending on the level of

hydrophobicity, moderately hydrophobic drugs can be solubilized by liposomes if the drug becomes encapsulated or intercalated within the liposome. Hydrophobic drugs can also be solubilized by liposomes if the drug molecule becomes an integral part of the lipid bilayer membrane, and in this case, the hydrophobic drug is dissolved in the lipid portion of the lipid bilayer.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

The pharmaceutical formulation can be prepared by lyophilising a compound of formula (I), or sub-groups thereof. Lyophilisation refers to the procedure of freeze-drying a composition. Freeze-drying and lyophilisation are therefore used herein as synonyms.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Pharmaceutical compositions of the present invention for parenteral injection can also comprise pharmaceutically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The compositions of the present invention may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the

like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion. For intravenous administration, the solution can be dosed as is, or can be injected into an infusion bag (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

In another preferred embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the

gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragee cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

The compounds of the invention can also be formulated as solid dispersions. Solid dispersions are homogeneous extremely fine disperse phases of two or more solids. Solid solutions (molecularly disperse systems), one type of solid dispersion, are well known for use in pharmaceutical technology (see (Chiou and Riegelman, J. Pharm. Sci., 60, 1281-1300 (1971)) and are useful in increasing dissolution rates and increasing the bioavailability of poorly water-soluble drugs.

This invention also provides solid dosage forms comprising the solid solution described above. Solid dosage forms include tablets, capsules and chewable tablets. Known excipients can be blended with the solid solution to provide the desired dosage form. For

example, a capsule can contain the solid solution blended with (a) a disintegrant and a lubricant, or (b) a disintegrant, a lubricant and a surfactant. A tablet can contain the solid solution blended with at least one disintegrant, a lubricant, a surfactant, and a glidant. The chewable tablet can contain the solid solution blended with a bulking agent, a lubricant, and if desired an additional sweetening agent (such as an artificial sweetener), and suitable flavours.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the formula (I) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within this range, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1

microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 miligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Protein Kinase Inhibitory Activity

The activity of the compounds of the invention as inhibitors of protein kinase A and protein kinase B can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC50 value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1 μM, more preferably less than 0.1 μM, against protein kinase B.

It has also been found that many compounds of the formula (I) have low hERG activity and a good separation between PHB/PKA activity and hERG activity.

Preferred compounds of the formula (I) have mean IC_{50} values against hERG that are greater than 30 times, or greater than 40 times, or greater than 50 times the IC_{50} values of the compounds in cellular proliferation assays. Preferred compounds of the formula (I) have mean IC_{50} values against hERG that are greater than 5 μM, more particularly greater than 10 μM, and more preferably greater than 15 μM. Some compounds of the invention have mean IC_{50} values against hERG that are greater than 30 μM, or greater than 40 μM, or greater than 50 μM.

Therapeutic Uses

Prevention or Treatment of Proliferative Disorders

The compounds of the formula (I) are inhibitors of protein kinase A and protein kinase B. As such, they are expected to be useful in providing a means of preventing the growth of or inducing apoptosis of neoplasias. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with deletions or inactivating mutations in PTEN or loss of PTEN expression or

rearrangements in the (T-cell lytmphocyte) TCL-1 gene may be particularly sensitive to PKB inhibitors. Tumours which have other abnormalities leading to an upregulated PKB pathway signal may also be particularly sensitive to inhibitors of PKB. Examples of such abnormalities include but are not limited to overexpression of one or more PI3K subunits, over-expression of one or more PKB isoforms, or mutations in PI3K, PDK1, or PKB which lead to an increase in the basal activity of the enzyme in question, or upregulation or overexpression or mutational activation of a growth factor receptor such as a growth factor selected from the epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), platelet derived growth factor receptor (PDGFR), insulin-like growth factor 1 receptor (IGF-1R) and vascular endothelial growth factor receptor (VEGFR) families.

It is also envisaged that the compounds of the invention will be useful in treating other conditions which result from disorders in proliferation or survival such as viral infections, and neurodegenerative diseases for example. PKB plays an important role in maintaining the survival of immune cells during an immune response and therefore PKB inhibitors could be particularly beneficial in immune disorders including autoimmune conditions.

Therefore, PKB inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

PKB inhibitors may also be useful in diseases resulting from insulin resistance and insensitivity, and the disruption of glucose, energy and fat storage such as metabolic disease and obesity.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, endometrium, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukaemia, acute lymphocytic leukaemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example acute and chronic myelogenous leukaemias, myelodysplastic syndrome, or promyelocytic leukaemia; thyroid follicular cancer; a tumour of

mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

A further subset of cancers includes breast cancer, ovarian cancer, prostate cancer, endometrial cancer and glioma.

It is also possible that some protein kinase B inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine of an inhibitor that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development. Examples of such combinations are set out below.

<u>Immune Disorders</u>

Immune disorders for which PKA and PKB inhibitors may be beneficial include but are not limited to autoimmune conditions and chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease.

<u>Other Therapeutic Uses</u>

PKB plays a role in apoptosis, proliferation, differentiation and therefore PKB inhibitors could also be useful in the treatment of the following diseases other than cancer and those associated with immune dysfunction; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example

Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases.

Methods of Treatment

It is envisaged that the compounds of the formula (I) and sub-groups thereof as defined herein will be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by protein kinase A and/or protein kinase B. Examples of such disease states and conditions are set out above.

The compounds are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a pulsatile or continuous manner.

A typical daily dose of the compound of formula (I) can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 5 nanograms to 25 milligrams per kilogram of bodyweight, and more usually 10 nanograms to 15 milligrams per kilogram (e.g. 10 nanograms to 10 milligrams, and more typically 1 microgram per kilogram to 20 milligrams per kilogram, for example 1 microgram to 10 milligrams per kilogram) per kilogram of bodyweight although higher or lower doses may be administered where required. The compound of the formula (I) can be administered on a daily basis or on a repeat basis every 2, or 3, or 4, or 5, or 6, or 7, or 10 or 14, or 21, or 28 days for example.

The compounds of the invention may be administered orally in a range of doses, for example 1 to 1500 mg, 2 to 800 mg, or 5 to 500 mg, e.g. 2 to 200 mg or 10 to 1000 mg, particular examples of doses including 10, 20, 50 and 80 mg. The compound may be administered once or more than once each day. The compound can be administered continuously (i.e. taken every day without a break for the duration of the treatment regimen). Alternatively, the compound can be administered intermittently, i.e. taken continuously for a given period such as a week, then discontinued for a period such as a week and then taken continuously for another period such as a week and so on throughout the duration of the treatment regimen. Examples of treatment regimens involving intermittent administration include regimens wherein administration is in cycles of one week on, one week off; or two weeks on, one week off; or three weeks on, one week off; or two weeks on, two weeks off; or four weeks on two weeks off; or one week on three weeks off - for one or more cycles, e.g. 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more cycles.

In one particular dosing schedule, a patient will be given an infusion of a compound of the formula (I) for periods of one hour daily for up to ten days in particular up to five days for one week, and the treatment repeated at a desired interval such as two to four weeks, in particular every three weeks.

More particularly, a patient may be given an infusion of a compound of the formula (I) for periods of one hour daily for 5 days and the treatment repeated every three weeks.

In another particular dosing schedule, a patient is given an infusion over 30 minutes to 1 hour followed by maintenance infusions of variable duration, for example 1 to 5 hours, e.g. 3 hours.

In a further particular dosing schedule, a patient is given a continuous infusion for a period of 12 hours to 5 days, an in particular a continuous infusion of 24 hours to 72 hours.

Ultimately, however, the quantity of compound administered and the type of composition used will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds as defined herein can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents or treatments that may be

administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include but are not limited to:

- Topoisomerase I inhibitors
- Antimetabolites
- Tubulin targeting agents
- DNA binder and topoisomerase II inhibitors
- Alkylating Agents
- Monoclonal Antibodies.
- Anti-Hormones
- Signal Transduction Inhibitors
- Proteasome Inhibitors
- DNA methyl transferases
- Cytokines and retinoids
- Chromatin targeted therapies
- Radiotherapy, and,
- Other therapeutic or prophylactic agents; for example agents that reduce or alleviate some of the side effects associated with chemotherapy. Particular examples of such agents include anti-emetic agents and agents that prevent or decrease the duration of chemotherapy-associated neutropenia and prevent complications that arise from reduced levels of red blood cells or white blood cells, for example erythropoietin (EPO), granulocyte macrophage-colony stimulating factor (GM-CSF), and granulocyte-colony stimulating factor (G-CSF). Also included are agents that inhibit bone resorption such as bisphosphonate agents e.g. zoledronate, pamidronate and ibandronate, agents that suppress inflammatory responses (such as dexamethazone, prednisone, and prednisolone) and agents used to reduce blood levels of growth hormone and IGF-I in acromegaly patients such as synthetic forms of the brain hormone somatostatin, which includes octreotide acetate which is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Further included are agents such as leucovorin, which is used as an antidote to drugs that decrease levels of folic acid, or folinic acid it self and agents such as megestrol acetate which can be used for the treatment of side-effects including oedema and thromoembolic episodes.

Each of the compounds present in the combinations of the invention may be given in individually varying dose schedules and via different routes.

Where the compound of the formula (I) is administered in combination therapy with one, two, three, four or more other therapeutic agents (preferably one or two, more preferably one), the compounds can be administered simultaneously or sequentially. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) and one, two, three, four or more other therapeutic agents can be, for example, formulated together in a dosage form containing two, three, four or more therapeutic agents. In an alternative, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

A person skilled in the art would know through his or her common general knowledge the dosing regimes and combination therapies to use.

Methods of Diagnosis

Prior to administration of a compound of the formula (I), a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against protein kinase A and/or protein kinase B.

For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to up-regulation of PKA and/or PKB or to sensitisation of a pathway to normal PKA and/orPKB activity, or to upregulation of a signal transduction component upstream of PKA and/or PKB such as, in the case of PKB, P13K, GF receptor and PDK 1 & 2.

Alternatively, a biological sample taken from a patient may be analysed for loss of a negative regulator or suppressor of the PKB pathway such as PTEN. In the present context, the term "loss" embraces the deletion of a gene encoding the regulator or suppressor, the truncation of the gene (for example by mutation), the truncation of the transcribed product of the gene, or the inactivation of the transcribed product (e.g. by point mutation) or sequestration by another gene product.

The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of PKA and/or PKB. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify mutations of PKA and/or PKB. The term marker also includes markers which are characteristic of up regulation of PKA and/or PKB, including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins.

The above diagnostic tests and screens are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, or urine.

Identification of an individual carrying a mutation in PKA and/or PKB or a rearrangement of TCL-1or loss of PTEN expression may mean that the patient would be particularly suitable for treatment with a PKA and/or PKB inhibitor. Tumours may preferentially be screened for presence of a PKA and/or PKB variant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody.

Methods of identification and analysis of mutations and up-regulation of proteins are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridisation.

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc., or Innis, M.A. et-al., eds. PCR Protocols: a guide to methods and applications, 1990, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook et al., 2001, 3rd Ed, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference.

An example of an in-situ hybridisation technique for assessing mRNA expression would be fluorescence in-situ hybridisation (FISH) (see Angerer, 1987 Meth. Enzymol., 152: 649).

Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) pre-hybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce non-specific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labelled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in Molecular Diagnosis of Cancer, Methods and Protocols, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: Methods in Molecular Medicine.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtitre plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow

cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques for detection of upregulation of PKB, or detection of PKB variants could be applicable in the present case.

Therefore all of these techniques could also be used to identify tumours particularly suitable for treatment with PKA and/or PKB inhibitors.

For example, as stated above, PKB beta has been found to be upregulated in 10 – 40% of ovarian and pancreatic cancers (Bellacosa et al 1995, Int. J. Cancer 64, 280 – 285; Cheng et al 1996, PNAS 93, 3636-3641; Yuan et al 2000, Oncogene 19, 2324 – 2330). Therefore it is envisaged that PKB inhibitors, and in particular inhibitors of PKB beta, may be used to treat ovarian and pancreatic cancers.

PKB alpha is amplified in human gastric, prostate and breast cancer (Staal 1987, PNAS 84, 5034 – 5037; Sun et al 2001, Am. J. Pathol. 159, 431 –437). Therefore it is envisaged that PKB inhibitors, and in particular inhibitors of PKB alpha, may be used to treat human gastric, prostate and breast cancer.

Increased PKB gamma activity has been observed in steroid independent breast and prostate cell lines (Nakatani et al 1999, J. Biol. Chem. 274, 21528 – 21532). Therefore it is envisaged that PKB inhibitors, and in particular inhibitors of PKB gamma, may be used to treat steroid independent breast and prostate cancers.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the following abbreviations may be used.

AcOH	acetic acid
BOC	*tert*-butyloxycarbonyl
DBU	2,3,4,6,7,8,9,10-octahydropyrimidol[1,2-a]azepine
DMAW90	Solvent mixture: DCM: MeOH, AcOH, H_2O (90:18:3:2)
DMAW120	Solvent mixture: DCM: MeOH, AcOH, H_2O (120:18:3:2)
DMAW240	Solvent mixture: DCM: MeOH, AcOH, H_2O (240:20:3:2)

DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
EDC	1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide
Et_3N	triethylamine
EtOAc	ethyl acetate
Et_2O	diethyl ether
Fmoc	9-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
mCPBA	m-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
MOM	methoxymethyl
NaH	sodium hydride
nBuLi	n-butyl lithium
SiO_2	silica
THF	tetrahydrofuran
Z/Cbz	benzyloxycarbonyl

Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 instrument operating at 400.13 MHz, in DMSO-d_6 or MeOH-d_4 (as indicated) at 27 °C, unless otherwise stated and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity where s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad). The residual protic solvent was used as the internal reference.

In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using the system and operating conditions set out below. Where atoms with different isotopes are present and a single mass quoted, the mass quoted for the compound is the monoisotopic mass (i.e. ^{35}Cl; ^{79}Br etc.). Different systems were used, as described below, and these were equipped with, and were set up to run under, closely similar operating conditions. The operating conditions used are also described below.

<u>System description:</u>

<u>System 1 (analytical system):</u>

HPLC System: Waters 2795

Mass Spec Detector:	Micromass Platform LC
PDA Detector:	Waters 2996 PDA

System 2 (preparative and analytical system):

HPLC System:	Waters Fractionlynx system
Mass Spec Detector:	Waters ZQ
PDA Detector:	Waters 2996 PDA

System 3 (preparative and analytical system):

HPLC System:	Agilent 1100 system
Mass Spec Detector:	LC/MSD
UV Detector:	Agilent MWD

Operating conditions:

Acidic analytical conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	5-95% eluent B over 3.5 minutes (over 15 minutes w/ column 2)
Flow:	0.8 ml/min
Column 1:	Phenomenex Synergi 4μ MAX-RP 80A, 2.0 x 50 mm
Column 2:	Phenomenex Synergi 4μ MAX-RP 80A, 2.0 x 150 mm

Basic analytical conditions:

Eluent A:	H_2O (10mM NH_4HCO_3 buffer adjusted to pH=9.2 with NH_4OH)
Eluent B:	CH_3CN
Gradient:	5-95% eluent B over 3.5 minutes
Flow:	0.8 ml/min
Column:	Phenomenex Gemini 5μ 2.0 x 50 mm

MS conditions (Waters systems):

Capillary voltage:	3.6 kV (3.40 kV on ES negative)
Cone voltage:	25 V
Source Temperature:	120 °C
Scan Range:	125-800 amu

Ionisation Mode:	ElectroSpray Positive, Negative or Positive & Negative

MS conditions (Agilent systems):

Capillary voltage:	4000 V (3500 V on ES Negative)
Fragmentor/Gain:	150 / 1
Drying gas Temp/flow:	350 °C / 13.0 Lmin^{-1}
Nebuliser pressure:	50 psig
Scan Range:	125-800 amu
Ionisation Mode:	ElectroSpray Positive or Negative

The starting materials for each of the Examples are commercially available unless otherwise specified.

A. GENERAL SYNTHETIC METHODS

METHOD A

A1. Amide coupling (acid chloride method)

A mixture of a carboxylic acid (1 equivalent) and thionyl chloride (excess, typically 1-5ml) was stirred and held at reflux for 1-6 hours. The reaction was allowed to cool then concentrated *in vacuo* and re-concentrated from a suitable organic solvent (e.g. dichloromethane). The residue was then dissolved in a suitable organic solvent (e.g. tetrahydrofuran) and added dropwise to a stirred mixture of amine (1 equivalent), triethylamine (1-3 equivalents) and suitable organic solvent (e.g. tetrahydrofuran) at 0-25 °C. After stirring for 5-72 hours, the mixture was typically diluted with ethyl acetate and washed with saturated brine (and any other suitable aqueous inorganic solution). The organic layer was reduced to dryness *in vacuo* and the product was either used crude or purified by column chromatography on silica (eluting with mixtures of ethyl acetate in petroleum ether). Occasionally, a solid precipitated upon aqueous work up; this was filtered and shown to contain product and was typically used without further purification.

A2. Amide coupling (EDC, HOBt method)

To a stirred solution of the acid or sodium salt (1 equivalent) in DMF (10 ml) was added 1-hydroxybenzotriazole (1.2 equivalents), the amine (1-1.2 equivalents) and either diisopropylethylamine or triethylamine (1.2-2.2eq) followed by N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.2 equivalents). The reaction mixture

was either stirred at room temperature or heated at 50-60 °C overnight. The mixture was diluted with ethyl acetate and washed with excess water/aqueous saturated sodium bicarbonate solution, the organic layer was separated and the solvent removed *in vacuo* to afford the product. The product was either taken on crude or purified by column chromatography on silica (eluting with mixtures of ethyl acetate in petroleum ether).

A3. Amide coupling (acid chloride using polymer supported reagents)

To a solution of amine (1 equivalent) in solvent (e.g. DCM), was added polymer supported diisopropylethylamine (3 equivalents) and acid chloride (1 equivalent). The reaction was left for 24-50 hours without stirring before quenching. Polymer supported isocyanate and polymer supported tris(hydroxymethyl)aminomethane (trisamine) were added, and the reaction mixture was left for a further 3-18 hours before filtering. The filtrate was concentrated *in vacuo* to yield product which was used directly without further purification.

METHOD B1

Suzuki Coupling

A mixture of aryl chloride, bromide or iodide (1 equivalent), inorganic base (typically potassium carbonate or potassium phosphate, 2-6 equivalents), catalyst (bis(tri-t-butylphosphine)palladium (0) for coupling of aryl chlorides; tetrakis(triphenylphosphine)palladium (0) for coupling of aryl bromides or iodides) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.1-1.5 equivalents) in ethanol/ methanol/ toluene/ water (ca. equal proportions) was irradiated in a CEM Explorer™ microwave to 80-145 °C for 15-30 minutes using $\leq$ 100 watts power. The reaction was either concentrated *in vacuo* or directly partitioned between ethyl acetate and 2N NaOH or water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were on occasions washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. In some cases the product precipitated out during work up, this was collected by filtration. If as this stage there was a significant amount of residual starting material, fresh reactants and reagents would be added and the reaction irradiated then worked up for a second time. The crude product was purified by column chromatography (SiO_2), eluting with a mixture of dichloromethane/ methanol or dichloromethane/ methanol/ ammonia or dichloromethane/ methanol/ acetic acid/ H_2O and/ or via preparative HPLC to afford the desired compounds.

METHOD B2

Suzuki Coupling with Thermal Heating

Under this method, the Suzuki coupling exemplified in Method B1 was conducted as described in B1, but instead the reaction mixture was heated thermally from 50 °C to reflux for a period of 30 minutes to 8 hours.

METHOD C

Condensation (AcOH cyclisation)

A solution of the aniline-amide in acetic acid (typically 1-5ml) was irradiated in a CEM Explorer™ microwave to 120 °C for 10-30 minutes using ≤ 50 watts power. The reaction was then concentrated *in vacuo* and the product either used directly or purified by silica column chromatography eluting with dichloromethane/ methanol/ acetic acid/ H_2O or ethyl acetate/ petroleum ether to furnish the pure benzimidazole product.

METHOD D

D1. SNAR - mono nitro

A solution of phenol (1 equivalent), 4-fluoronitrobenzene (1 equivalent), potassium carbonate (2 equivalents) in dimethylformamide was heated to 100 °C for 1-5 hours. The reaction was then filtered under suction and washed with ethyl acetate. The liquors were washed with one or more aqueous solutions (selected from water, lithium chloride, sodium bicarbonate and saturated brine), before concentrating *in vacuo*. The biaryl ethers were either used thus or purified by silica column chromatography eluting with a mixture of ethyl acetate/ petrol.

D2. SNAR - nitroaniline

A solution of the phenol (1 equivalent), 4-chloro-2-aminonitrobenzene (1.1 equivalent), potassium carbonate (2 equivalents) in dimethylformamide was heated to 140 °C for 1-5 hours. The product was isolated by either work up method 1 or 2. Work up method 1: The reaction was then filtered under suction and washed with ethyl acetate. The liquors were washed with one or more aqueous solutions (selected from water, lithium chloride, sodium bicarbonate and saturated brine), before concentrating *in vacuo*. Work up method 2: The reaction was partitioned between ethyl acetate and water, the organic was washed with saturated brine, dried ($MgSO_4$) and concentrated *in vacuo*. The biaryl ethers were either

taken on crude or purified by silica column chromatography eluting with a mixture of ethyl acetate/ petroleum ether.

D3. SNAR - mono nitro – trial reactions

A solution of phenol (1 equivalent), 4-fluoronitrobenzene (1 equivalent), base (e.g. potassium carbonate or sodium hydride, 1-2 equivalents) in organic solvent (e.g. dimethylformamide or dimethylsulphoxide) was stirred at room temperature for 1-5 hours and at 100 °C for 1-18 hours. The reaction was then diluted with water and acidified with aqueous hydrochloric acid (2N) before extraction with ethyl acetate. The combined organic liquors were washed with 10% aqueous lithium chloride and saturated brine solution before drying ($MgSO_4$) and concentrating *in vacuo*. The residue was optionally combined with those from other such reactions and was purified using silica column chromatography eluting with ethyl acetate/ petroleum ether mixtures to furnish the desired compound with some impurity remaining.

D4. SNAR – mono nitro – amine displacement

A solution of 3-fluoronitrobenzene (1 equivalent) and amine (1-10 equivalents) in dimethylsulphoxide was heated to 100 °C for 4 days. The reaction was subjected to an aqueous work up, washing with 10% aqueous lithium chloride solution; the organic liquors were concentrated *in vacuo* to furnish the crude material that was purified by silica column chromatography eluting with 10-50% ethyl acetate/ petroleum ether to furnish the desired compound.

METHOD E

Hydrogenation

A solution of nitrobenzene and palladium on carbon (typically 10% by weight relative to nitrobenzene) in ethanol, optionally with acetic acid co-solvent (10% volume relative to ethanol), was hydrogenated at atmospheric pressure and at room temperature for 1-18 hours. When the requisite volume of hydrogen had been consumed, the reaction was filtered under suction using either a celite pad or glass fibre filter paper before concentrating to furnish either the free base or acetate salt of the desired aniline. This material was typically used crude, occasionally purified by silica column chromatography eluting with ethyl acetate/ petroleum ether mixtures.

METHOD F1

Buchwald Amination

A solution of aryl bromide (1 equivalent), amine (1.5 equivalents), tris(dibenzylideneacetone)dipalladium (0) (5 mol%), rac-2,2-bis(diphenylphosphino)-1,1-binaphthyl (BINAP, 10 mol%) and sodium tert-butoxide (3 equivalents) in dioxane were heated to 65 °C for 1-4 hours under nitrogen. The reaction was allowed to cool then water was added and extracted into ethyl acetate (x2). The combined liquors could then be concentrated *in vacuo* and used thus or purified by silica column chromatography eluting with ethyl acetate/ petroleum ether mixtures. Alternatively the product could be extracted into aqueous hydrochloric acid solution (1N), basified with suitable base (e.g. aqueous sodium hydrogen carbonate solution) and back extracted into ethyl acetate. This product could be used thus or purified as described above.

METHOD F2

A mixture of an aryl halide (preferably iodide, 1 equivalent), amine (1.3 equivalents), copper (I) iodide (0.1 equivalents), trans diaminocyclohexane (0.2 equivalents) and potassium carbonate (2 equivalents) in dioxane was heated, under nitrogen, to 110 °C overnight. The reaction was then allowed to cool and dichloromethane and water was added. The mixture was filtered under suction and the organic layer was separated. These liquors were washed with 5% citric acid then brine before drying ($MgSO_4$) and concentrating *in vacuo*. The residue was purified by silica column chromatography furnishing the clean product.

METHOD G

SNAR - para nitrile

4-fluorobenzonitrile (1 equivalent) was dissolved in anhydrous DMF (0.7-8 ml) in a React-i-vial. To this solution was added the phenol (1.1 equivalent) followed by potassium carbonate (1.1 equivalent). The suspension was heating at 150 °C with stirring for 16 hours and was then allowed to cool to room temperature. The reaction mixture was diluted with water and extracted twice with DCM. The organics were combined, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The products were taken through to the next step without further purification.

METHOD H

Nitrile Hydrolysis

The benzonitrile (1 equivalent) was suspended in a 1:1 mixture of ethanol and water (44 ml). To this suspension was added solid sodium hydroxide (12.7 equivalents). The suspension was heated at 100 °C with stirring for 16 hours. The resulting solution was allowed to cool to room temperature and then evaporated to dryness *in vacuo*. The residue was dissolved in water and washed twice with diethyl ether. The aqueous was acidified using concentrated HCl to either pH 1 (in which case the solid precipitate was filtered and dried) or pH 4 (in which case the aqueous was extracted twice with ethyl acetate, the organics were combined, dried ($MgSO_4$) and evaporated to dryness *in vacuo*). The products were taken through to the next step without further purification.

METHOD I

Mitsunobu reaction

To a solution of resorcinol monobenzylate (1 equivalent), an alkyl alcohol (1.1 equivalents) and triphenylphosphine (1.3 equivalents) in THF at 0 °C under nitrogen was added dropwise diisopropyl azodicarboxylate (1.1 equivalents). The reaction was stirred thus for 30 minutes then allowed to warm to room temperature. After 1-18 hours at room temperature, the reaction was concentrated *in vacuo* before tituration/ crystallisation with suitable solvents (typically petroleum ether and optionally diethyl ether). The solid was then filtered under suction and the organic liquors were concentrated to furnish the desired ether as an oil.

METHOD J

Ester Hydrolysis

To the ester (1 equivalent) was added methanol (25 ml) and water (25 ml). Sodium hydroxide (1.1 equivalents) was added as a solid and the reaction mixture was heated at 50 °C with stirring for 20.5 hours. The reaction mixture was allowed to cool to room temperature and evaporated to dryness *in vacuo*. The products were taken through to the next step without further purification.

METHOD K

Benzoate Deprotection

A solution of the benzylresorcinol in ethanol and aqueous sodium hydroxide (2N, 1:1) was stirred at room temperature for 18 hours. The reaction was then acidified with aqueous hydrochloric acid (2N) and the product extracted into ether (x3). The combined liquors

were washed with saturated brine then dried ($MgSO_4$) before concentrating *in vacuo*. The product was used thus or purified using silica column chromatography eluting with ethyl acetate/ petroleum ether mixtures.

METHOD L

FMOC Deprotection

To a solution of the FMOC protected amine in suitable organic solvent (typically dichloromethane) was added a scavenger for the fluorenylmethyl cation (e.g. morpholine, piperadine or polymer supported thiol resin, excess) then 2,3,4,6,7,8,9,10-octahydropyrimidol[1,2-a]azepine (DBU, catalytic amount). The mixture was stirred or shaken thus for 4-72 hours. If the reaction was not complete at this stage, an additional volume of DBU was added and the reaction stirred for a further 1-18 hours. Any solid was removed by filtration and the solvent removed *in vacuo*. The crude product was used directly or purified by ion exchange chromatography (SCX, eluting with methanolic ammonia) and/ or by silica column chromatography typically using a mixture of dichloromethane, methanol, acetic acid and H_20.

METHOD M

Boc and/or MOM Deprotection

To the protected amine, optionally dissolved in a suitable organic solvent (typically dichloromethane), was added a strong organic (e.g. trifluoroacetic acid) or inorganic (e.g. hydrochloric acid in 1,4-dioxane) acid. This mixture was stirred at room temperature for between 10 minutes and 18 hours to furnish the crude amine as a salt. If necessary, purification could be achieved via silica column chromatography using a mixture of dichloromethane, methanol, acetic acid and H_20 or dichloromethane, methanol and ammonia, and/ or via ion exchange chromatography and/ or by preparative HPLC.

METHOD N

Boc Protection

To a solution of protected amine in a suitable organic solvent (e.g. dichloromethane, DMF, THF) was added a base (e.g. triethylamine, aqueous sodium hydroxide or aqueous sodium bicarbonate, 1 to excess equivalents) and di-tert-butyl dicarbonate (1 to excess equivalents). This mixture was stirred at room temperature for 30 minutes to 18 hours before aqueous

workup. The crude product was optionally purified by silica column chromatography eluting with ethyl acetate/ petroleum ether to furnish the desired compound.

METHOD O

O1. Z Deprotection – Bromocatechol borane

B-Bromocatecholborane (1.5 equivalents) was added to a solution of the protected amine (1 equivalent) and the reaction mixture was stirred at room temperature for 17 hours. The dichloromethane was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic layer was extracted with water and the combined aqueous layers were basified with 2N NaOH solution and extracted in to ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by silica column chromatography typically using a mixture of dichloromethane, methanol, acetic acid and H_20.

O2. Z Deprotection – HBr

The protected amine was dissolved in 45% HBr in AcOH solution and then stirred at room temperature for 3 hours. The reaction mixture was then evaporated to dryness *in vacuo* and the residue was dissolved in methanol and passed through an ion exchange column. The crude product was then used in the next step without further purification.

METHOD P

P1. Dealkylation (BBr_3) – after Buchwald

To a solution of the methyl ether in dichloromethane under nitrogen at 0 °C was added boron tribromide (2 equivalents, 1M solution in dichloromethane), the reaction mixture was stirred at room temperature for approximately 18 hours. Reaction was cooled to 0 °C and quenched with MeOH, partitioned between dichloromethane and water, aqueous was basified with saturated aqueous sodium bicarbonate and extracted with dichloromethane. Organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to yield product which was used without further purification.

P2. Dealkylation (BBr_3) – final compound

To a solution or suspension of the methyl ether in dichloromethane was added excess boron tribromide in dichloromethane. After stirring at room temperature for 1-18 hours the reaction was quenched with methanol then concentrated *in vacuo*. Purification by ion

exchange chromatography (NH_2, eluting with methanolic hydrochloric acid or methanolic ammonia) and/ or preparative HPLC and/ or silica column eluting with dichloromethane/ methanol/ acetic acid/ H_2O mixtures or dichloromethane/ ammonia mixtures furnished the demethylated compound.

METHOD Q

Tin (II) Chloride reduction

A solution of the substituted nitrobenzene (1 equivalent) and tin (II) chloride (5-10 equivalents) in ethanol (typically 1-5ml) was irradiated in a CEM Explorer™ microwave to 140 °C for 10 minutes using >50 watts power. The reaction was then basified to pH8 using saturated aqueous sodium bicarbonate, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo* to yield product with was taken on without further purification.

METHOD R

Ritter Reaction

A solution of 2-(4-bromophenyl)oxirane (1 equivalent) in methylamine (10 equivalent, 33% by weight in ethanol) was stirred at room temperature for 17-24 hours. The reaction was concentrated in vacuo and purified by silica column eluting with DMAW 120 to yield 1-(4-Bromo-phenyl)-2-methylamino-ethanol.
To a solution of 1-(4-Bromo-phenyl)-2-methylamino-ethanol (1 equivalent) in benzonitrile (5ml) under nitrogen was added aluminium chloride (3 equivalents); the reaction was heated at 50 °C for 12-18 hours then 70 °C for a further 45-60 hours. Once cooled the reaction was quenched with water, partitioned between ethyl acetate and 2N NaOH, organic extracts combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by ion exchange column chromatography to furnish the desired product.

METHOD S

Sonogashira

To a mixture of alkyne (1.2 equivalents), aryl halide (1 equivalent), triethylenediamine (3 equivalents) in acetonitrile was added palladium acetate (2-5 mol %). The reaction mixture was stirred under air for 1-3 days, filtered and the filtrate was concentrated to yield crude product.

METHOD T

Dimethylsulphonamide protecting group removal (with optional, concomitant Boc removal)

To a solution of the substrate dissolved in methanol was added a catalytic or excess amount of concentrated hydrochloric acid. The mixture was then heated to reflux for 1-6 hours until the starting material had been consumed. The reaction mixture was then concentrated or basified with saturated inorganic base (e.g. sodium bicarbonate solution), extracted into a suitable organic solvent (e.g. dichloromethane or ethyl acetate) then dried and concentrated. The crude material was then purified on silica and/ or preparative HPLC to furnish the deprotected product.

METHOD U

Imidazole formation

An alkyl acid (typically Preparation K) was converted to the arylimidazole using, for example, 2-bromoacetophenone using the method detailed in the patent application US2004/0077640A1.

METHOD V

Preparation of hydrochloride salt

The starting material was dissolved in AcOEt or MeOH and then treated with 1 mol. equivalent of HCl (4N solution in dioxane). The product was obtained by evaporating to dryness or collection by filtration.

METHOD W

Formation of a benzoxazole

A solution of an amido-phenol (e.g. 4-(4-bromo-phenyl)-4-(2-hydroxy-phenylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester) in acetic acid was heated at reflux for 1 hour to overnight. The resultant solution was concentrated *in vacuo* and the product used directly or purified by silica column chromatography eluting with dichloromethane/ methanol/ acetic acid/ water or ethyl acetate/ petroleum ether to furnish the pure benzoxazole product.

METHOD X

Methylation

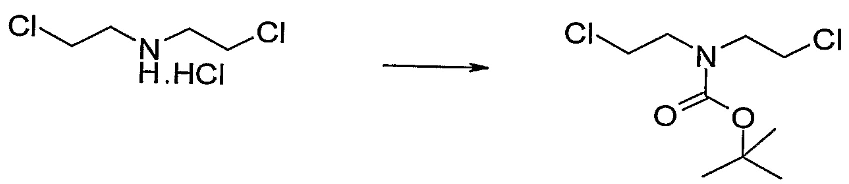
To a solution of secondary amine in DMF was added dropwise a solution of iodomethane (2.0 M tert-butyl methyl ether) in DMF. The reaction mixture was stirred at room temperature for 3 hours and filtered. The filtrate was concentrated and purified through an NH2 ion exchange column, the crude product was purified further by preparative HPLC.

SYNTHESIS OF INTERMEDIATES

PREPARATION A

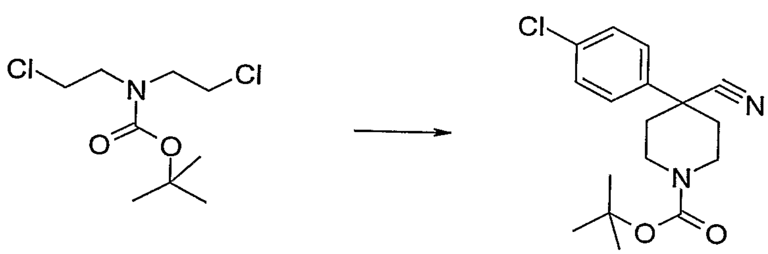
4-(4-Chloro-phenyl)-piperidine-1,4-dicarboxylic acid mono-(9H-fluoren-9-ylmethyl) ester

A1. Bis-(2-chloro-ethyl)-carbamic acid *tert*-butyl ester



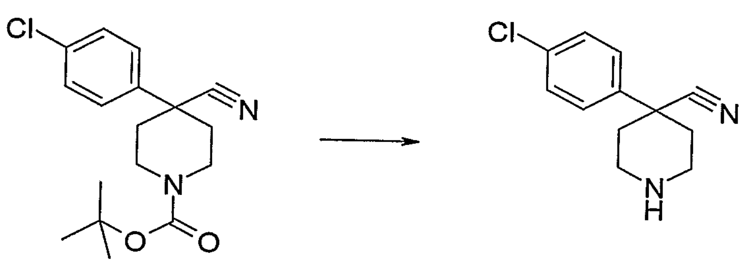
Bis-(2-chloro-ethyl)-carbamic acid *tert*-butyl ester was made using a method described in J. Chem. Soc., Perkin Trans 1, 2000, p3444-3450.

A2. 4-(4-Chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid tert-butyl ester



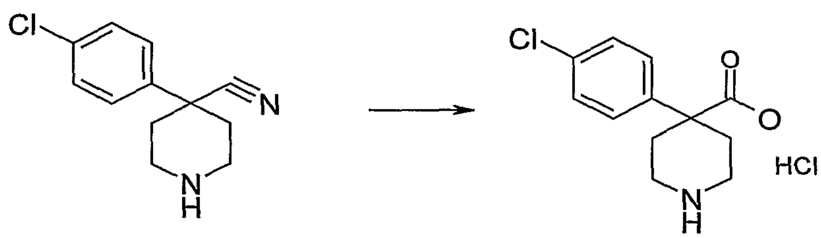
4-(4-Chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid tert-butyl ester was made using a method described in WO2004/022539.

A3. 4-(4-Chloro-phenyl)-piperidine-4-carbonitrile



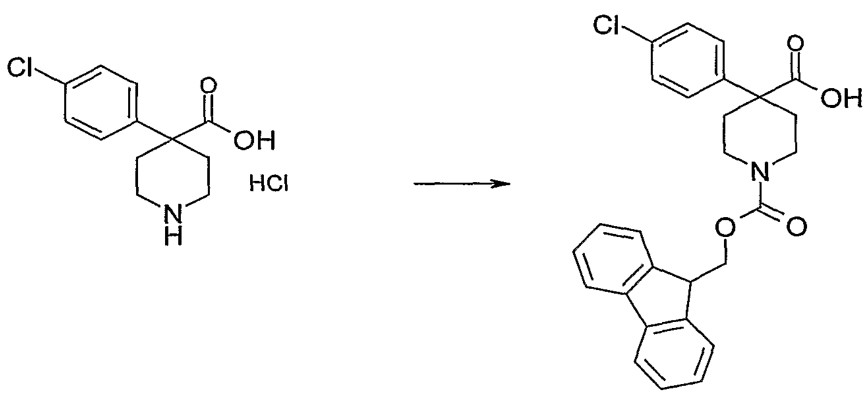
A solution of 4-(4-chloro-phenyl)-4-cyano-piperidine-1-carboxylic acid tert-butyl ester (15g, 47mmol), trifluoroacetic acid (30ml) and dichloromethane (30ml) was stirred at room temperature for 30 minutes. The reaction was then concentrated *in vacuo* and re-concentrated from dichloromethane (x3). The residue was then dissolved in dichloromethane, washed with saturated aqueous bicarbonate solution and concentrated again *in vacuo*. The desired compound was obtained as a white solid (11.4g, 100% yield)

A4. 4-(4-Chloro-phenyl)-piperidine-4-carboxylic acid



A solution of 4-(4-chloro-phenyl)-piperidine-4-carbonitrile in aqueous hydrochloric acid (4N, 500ml) was refluxed for 3 days, adding additional concentrated acid as required. The reaction was then concentrated and dried in a vacuum oven to furnish the desired compound as a beige solid (14.7g, 100% yield)

A5. 4-(4-Chloro-phenyl)-piperidine-1,4-dicarboxylic acid mono-(9H-fluoren-9-ylmethyl) ester



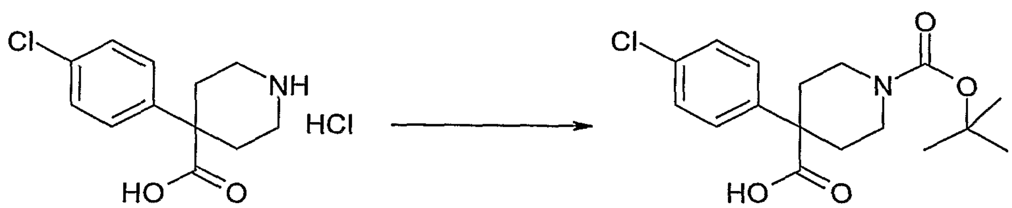
A mixture of 4-(4-chloro-phenyl)-piperidine-4-carboxylic acid (276mg, 1.0mmol), fluorenylmethyl succinimidyl carbonate (354mg, 1.1mmol), aqueous sodium hydroxide (2N, 2ml), water (3ml) and tetrahydrofuran (5ml) were stirred vigorously for 4 hours. The aqueous mixture was then acidified with aqueous hydrochloric acid (2N, pH<3) then extracted into ethyl acetate (x2). The combined liquors were washed with saturated brine

then dried ($MgSO_4$) and concentrated *in vacuo* to furnish the title compound contaminated with fluorenyl impurities (ca. 85% pure, 375mg).

PREPARATION B

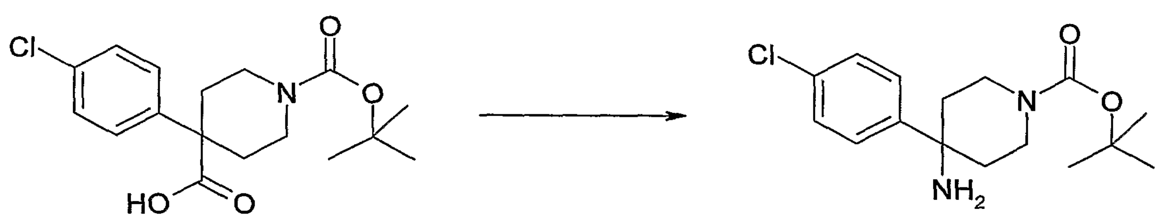
4-Amino-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester

B1. 4-(4-Chloro-phenyl)-piperidine-1,4-dicarboxylic acid mono-tert-butyl ester



A mixture of 4-(4-chloro-phenyl)-piperidine-4-carboxylic acid hydrochloride (1.4 g, 5.07 mmol), di-tert-butyl dicarbonate (1.21 g, 5.57 mmol), aqueous sodium hydroxide (2N, 10 ml), water (15 ml) and tetrahydrofuran (25 ml) were stirred vigorously for 18 hours. The aqueous mixture was then acidified with aqueous hydrochloric acid (2N, 11 ml) then extracted into ethyl acetate (x2). The combined liquors were washed with saturated brine then dried ($MgSO_4$) and concentrated *in vacuo* to furnish the title compound (1.47 g, 86%).

B2. 4-Amino-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester

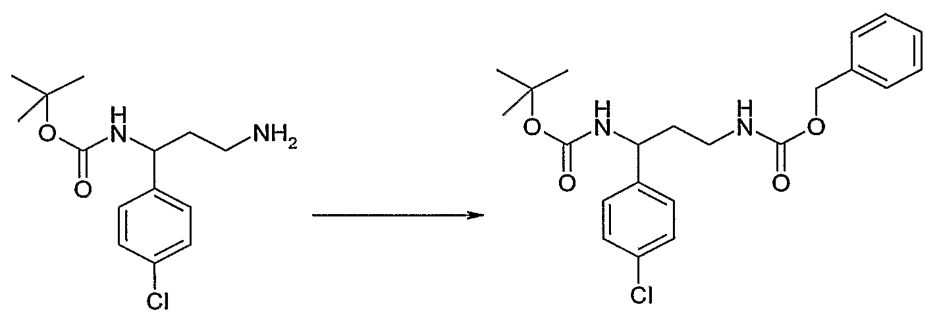


Isobutyl chloroformate (172 µl, 1.33 mmol) was added to a solution of 4-(4-chloro-phenyl)-piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (300 mg, 0.89 mmol) and triethylamine (247 µl, 1.77 mmol) in tetrahydrofuran (9 ml) at -10 °C, under an atmosphere of argon. After stirring for 1 hour, a solution of sodium azide (115 mg, 1.77 mmol) in water was added and the reaction mixture was allowed to reach room temperature and stirred for a further 20 hours. Water was then added and the aqueous phase extracted with diethyl ether (x2). The combined organics were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in toluene (20 ml) and stirred at 90 °C for 2 hours. The solution was then cooled and 10% HCl solution was added. The biphasic mixture was then warmed to 90 °C and stirred for 24

hours. The two phases were separated and the organic layer was evaporated to dryness. The residue was then dissolved in a mixture of THF (4 ml) and 2N NaOH solution (4.4 ml, 8.85 mmol) and di-tert-butyl dicarbonate (212 mg, 0.97 mmol) was added. The solution was stirred at room temperature for 17 hours and then partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was then separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by silica column chromatography eluting with ethyl acetate/ petroleum ether to furnish the desired compound (116 mg, 42%).

PREPARATION C

[3-tert-Butoxycarbonylamino-3-(4-chloro-phenyl)-propyl]-carbamic acid benzyl ester

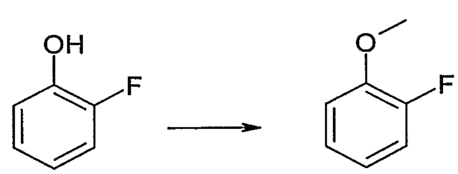


Benzylchloroformate (2.75 ml, 19.25 mmol) and triethylamine (4.88 ml, 101.2 mmol) were added sequentially to a solution of [3-Amino-1-(4-chloro-phenyl)-propyl]-carbamic acid tert-butyl ester (4.98 g, 17.5 mmol) in dichloromethane (175 ml). The reaction mixture was stirred at room temperature for 17 hours and then partitioned with water. The organic layer was then separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then used in the next step without further purification.

PREPARATION D

4-(2-Fluoro-3-methoxy-6-methoxymethoxy-benzoyl)-benzoic acid

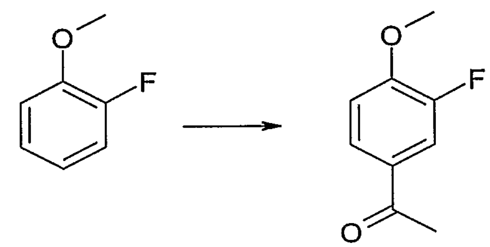
D1. 1-Fluoro-2-methoxy-benzene



To a slurry of NaH (28.8g, 0.60mol) in dry DMF (500ml) at 0 °C was added 2-fluoro phenol (50g, 0.446mol) slowly over a period of 30min and stirred for 1h at room

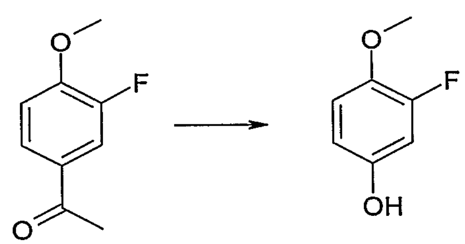
temperature. To this was added methyl iodide (190g, 1.33mol) and the reaction mixture was stirred for 16h under nitrogen and poured into ice-water (1.5L). The product was extracted with ethyl acetate (2 x 200ml), washed with water, brine and dried. The solvent was removed under vacuum to afford 55g (98%) of the title compound.

D2. 1-(3-Fluoro-4-methoxy-phenyl)-ethanone



To a slurry of $AlCl_3$ (63.5g, 0.476mol) in dry dichloromethane (500ml) under nitrogen was added acetyl chloride (37.3g, 0.476mol) and the mixture was stirred for 1h at room temperature. To this was added a solution of 1-fluoro-2-methoxybenzene (50g, 0.396mol) in dichloromethane (200ml) and the mixture was stirred at room temperature for 16h. This was then poured into ice-water (2L) and extracted with dichloromethane. The organic layer was washed with water, brine and dried. The solvent was removed under vacuum to afford 50g (75%) of the title compound.

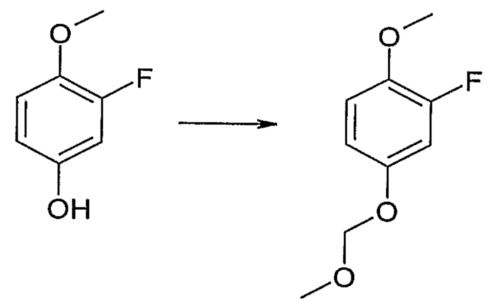
D3. 3-Fluoro-4-methoxy-phenol



To a solution of 1-(3-fluoro-4-methoxyphenyl)ethanone (50g, 0.297mol) in dichloromethane (1.5L) was added mCPBA (100g, 77%) and the reaction mixture was refluxed for 42h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was evaporated and the residue was taken up in 10% NaOH solution (250ml) and refluxed for 4h. The reaction mixture was cooled and washed with diethyl ether (3x200ml). The aqueous phase was acidified with 1.5N HCl and the product was extracted with ethyl acetate (2x200ml). The combined organic layer was washed with water, brine and dried.

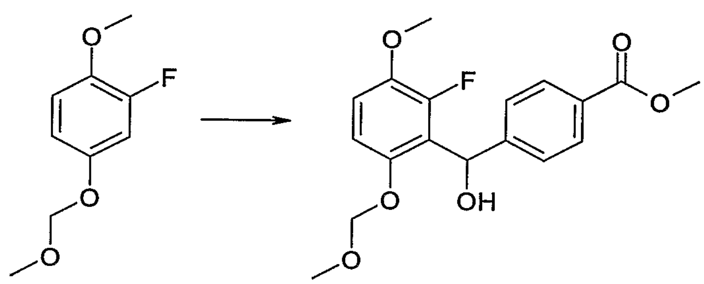
The solvent was removed under reduced pressure to afford 22g (52%) of the title compound.

D4. 2-Fluoro-1-methoxy-4-methoxymethoxy-benzene



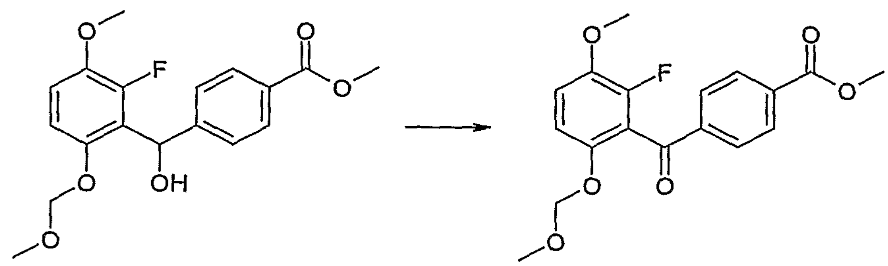
To a solution of 3-fluoro-4-methoxyphenol (10g, 0.070mol) in dry dichloromethane (200ml) at 0 °C was added diisopropylethylamine (21g, 0.14mol) followed by MOM-chloride (11.2g, 0.14mol). The reaction mixture was stirred at room temperature for 15h and diluted with water (200ml). The organic phase was separated, dried and evaporated to afford 7g (53%) of the title compound.

D5. 4-[(2-Fluoro-3-methoxy-6-methoxymethoxy-phenyl)-hydroxy-methyl]-benzoic acid methyl ester



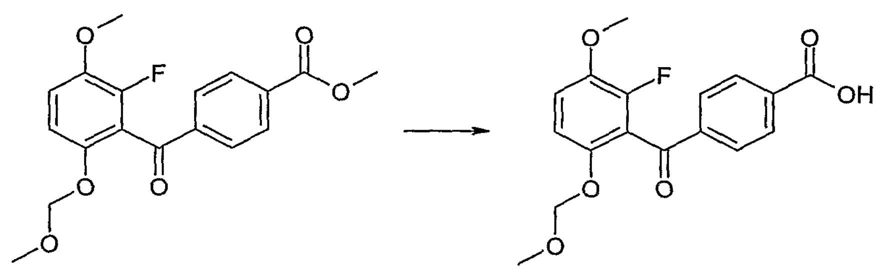
To a solution of 2-fluoro-1-methoxy-4-(methoxymethoxy)benzene (3.5g, 0.0185mol) in dry THF (70ml) at -78 °C was added n-BuLi (9.3ml, 3M, 0.028mol) and the mixture was stirred for 2h. To this was added a solution of methyl-4-formyl benzoate (4.6g, 0.028mol) in dry THF (20ml) and the mixture was slowly allowed to warm to room temperature over a period of 10h. Water (200ml) was added and the product was extracted with ethyl acetate (2x100ml). The combined organic phases were washed with water, brine and dried. The solvent was removed under vacuum and the residue was purified by flash chromatography (silica gel, 60-120 mesh) eluting with petroleum ether/ethyl acetate (8/2) to afford 2.4g (37%) of the title compound.

D6. 4-(2-Fluoro-3-methoxy-6-methoxymethoxy-benzoyl)-benzoic acid methyl ester



To a solution of methyl 4-[[2-fluoro-3-methoxy-6-(methoxymethoxy)-phenyl](hydroxy)methyl]benzoate (2.4g, 0.0068 mol) in dichloromethane (75 ml) was added Dess-Martin periodinane (5.8g, 0.0137 mol) and the mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with dichloromethane (100ml) and washed with 10% solution of sodium bicarbonate. The organic phase was dried and evaporated. The residue was purified by chromatography (silica gel, 60-120 mesh) eluting with petroleum ether/ethyl acetate (8/2) to afford 1.6g (67%) of the title compound.

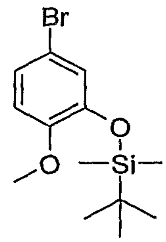
D7. 4-(2-Fluoro-3-methoxy-6-methoxymethoxy-benzoyl)-benzoic acid



To a solution of methyl 4-[2-fluoro-3-methoxy-6-(methoxymethoxy)-benzoyl]benzoate (1.6g, 0.0045mol) in methanol (20ml) was added water (5ml) followed by lithium hydroxide (0.2g, 0.009mol) and the mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue was acidified with 5% solution of citric acid. The solid precipitate was filtered, washed with water and dried under suction to afford 1.2g (80%) of the title compound.

PREPARATION E

(5-Bromo-2-methoxy-phenoxy)-tert-butyl-dimethyl-silane formation



A solution of 5-Bromo-2-methoxy-phenol (prepared from guaiacol using the method outlined in WO-0119785, 6.5g, 32mmol), tert-butyldimethyl chlorosilane (5.3g, 35mmmol) and imidazole (2.4g, 35mmol) in dimethylformamide (5ml) was stirred at room temperature. After 3 hours water was added and the reaction extracted into ethyl acetate. The organic liquors were washed with 10% aqueous lithium chloride solution (x2) and saturated brine before drying ($MgSO_4$) and concentration *in vacuo* to furnish the title compound as an orange oil (10.6g).

PREPARATION F

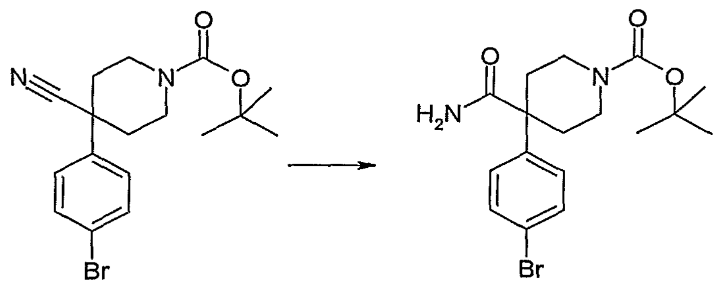
F. 4, 4-Dimethyl-piperidine

Lithium aluminium hydride (3.36g, 88.55 mmol) was suspended in anhydrous THF (89 ml) and the suspension was cooled to 0 °C. 4, 4-dimethylglutarimide (5g, 35.42 mmol) was partially dissolved in anhydrous THF (89 ml) and this was added dropwise to the suspension of lithium aluminium hydride, maintaining the temperature of the reaction mixture between 0 and 3 °C. The reaction mixture was then heated at 55 °C for 30 minutes. The reaction mixture was then cooled to 0 °C and an aqueous 1N sodium hydroxide solution (50 ml) was added dropwise. The reaction mixture was filtered through Celite, washing through with THF and water. The filtrate was evaporated *in vacuo* to remove most of the THF. The aqueous phase was extracted with diethyl ether. The organic phases were separated off, dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound as a yellow oil (2.41g, 60%).

PREPARATION H

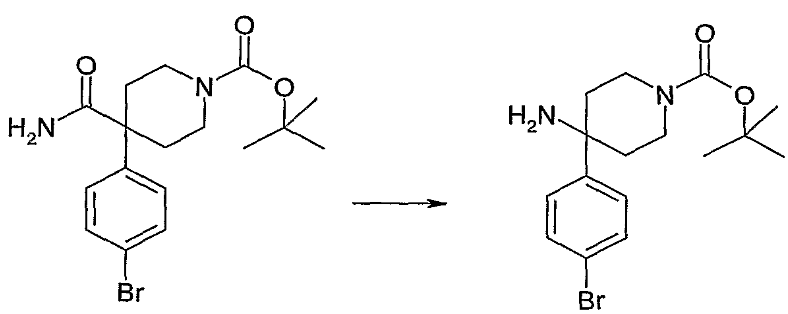
4-Amino-4-(4-bromo-phenyl)-piperidine-1-carboxylic acid tert-butylester

H1.4-(4-bromo-phenyl)-4-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester



To a mixture of 4-(4-bromo-phenyl)-4-cyano-piperidine-1-carboxylic acid tert-butyl ester (2.0 g, 5.48 mmol) in glacial acetic acid (5 ml) stirring at ambient temperature was added dropwise concentrated sulphuric acid (2.5 ml). The mixture was heated at 50 °C for 16 hours then cooled to ambient temperature. The mixture was diluted with water and then extracted with ethyl acetate. The organic portion was re-extracted with hydrochloric acid (2M) and the combined aqueous portions taken to pH~14 using sodium hydroxide (2M). To the resultant solution was added a solution of di-*tert*-butyl dicarbonate (1.89 g, 8.2 mmol) in dioxane (100 ml). The mixture was heated at 50 °C for 72 hours, cooled to ambient temperature and extracted with ethyl acetate (x2). The combined organic extracts were washed successively with saturated ammonium chloride solution and brine, dried ($MgSO_4$) and reduced *in vacuo* to give the title compound as an off-white solid (2.26g).

H2.4-amino-4-(4-bromo-phenyl)-piperidine-1-carboxylic acid tert-butylester



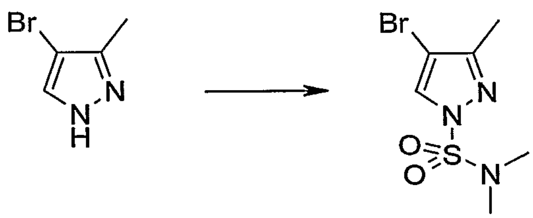
A mixture of 4-(4-bromo-phenyl)-4-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester (1.20g, 3.13 mmol) and [bis(trifluoroacetoxy)iodo]benzene (1.38g, 3.20mmol) in acetonitrile-water (1:1, 16 ml) was stirred at ambient for 18 hours and then diluted with water (50 ml). The mixture was extracted with ethyl acetate and the combined organic

extracts were washed successively with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$) and reduced *in vacuo* to give the title compound as brown oil (1.1 g, 99%).

PREPARATION I

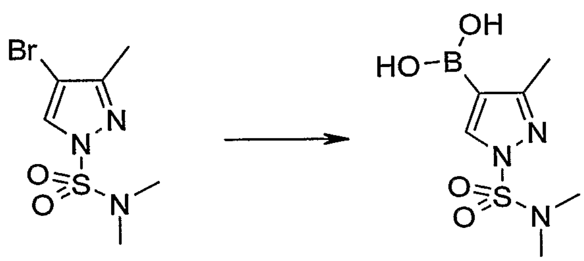
3-methyl-1-sulphonic acid dimethylamide-pyrazole-4-boronic acid

I1. 4-Bromo-3-methyl-pyrazole-1-sulphonic acid dimethylamide



1,4-Diazabicyclo[2.2.2]octane (DABCO, 3.83g, 34.1 mmol) and dimethylsulphamoylchloride (3.32ml, 31.0 mmol) were added sequentially to a solution of 4-bromo-3-methylpyrazole (5.0g, 31.0 mmol) in acetonitrile (50 ml) whilst stirring at room temperature. After 6 hours, the reaction was quenched with water then 2N HCl was added. The solution was extracted twice with ethyl acetate and the organic liquors were washed with brine before drying ($MgSO_4$) and concentrating *in vacuo*. The resultant oil was re-concentrated from diethylether twice to afford a white foam (6.7g, 81%).

I2. 3-methyl-1-sulphonic acid dimethylamide-pyrazole-4-boronic acid



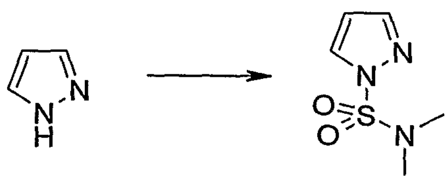
To a solution of 4-bromo-3-methyl-pyrazole-1-sulphonic acid dimethylamide (7.3g, 27.2 mmol) and triethylborate (6.9 ml, 40.8 mmol) in anhydrous tetrahydrofuran (80 ml) under a nitrogen atmosphere was added dropwise a solution of methyl lithium in ether (1.6M, 22 ml, 35.4 mmol) while the temperature was maintained below -55 °C. The reaction was stirred at this temperature for 20 minutes before allowing the reaction to warm to room temperature. After stirring thus overnight, the reaction was quenched by cautious addition

of hydrochloric acid (2N) before extraction of the product into 3 portions of ethyl acetate. The combined organic liquors were washed with brine before drying ($MgSO_4$) and concentrated *in vacuo* to furnish an oil. The product was purified on a 40+M silica Biotage column, eluting on a gradient 0-15% methanol/ dichloromethane to furnish the title compound as a pale yellow oil (4.2g, 66%).

PREPARATION J

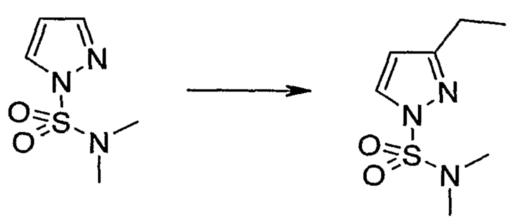
3-Ethyl-1-sulphonic acid dimethylamide-pyrazole-4-boronic acid

J1. Pyrazole-1-sulphonic acid dimethylamide



1,4-Diazabicyclo[2.2.2]octane (DABCO, 10.1g, 90.3 mmol) and dimethylsulphamoylchloride (8.8 ml, 82.9 mmol) were added sequentially to a solution of pyrazole (4.8g, 81.9 mmol) in acetonitrile (125 ml) whilst stirring at room temperature. After 18 hours, the reaction mixture was concentrated *in vacuo* and partitioned between water and ethyl acetate. The organic layer was removed and washed with hydrochloric acid (2N) and then brine before drying ($MgSO_4$) and concentrating *in vacuo* to furnish the title compound as a colourless oil (13.1g, 91%).

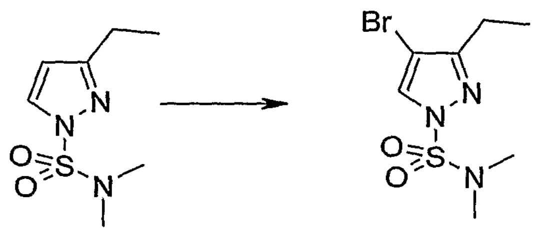
J2. 3-Ethyl-pyrazole-1-sulphonic acid dimethylamide



To a solution of pyrazole-1-sulphonic acid dimethylamide (13.1g, 74.9 mmol) in anhydrous tetrahydrofuran (100 ml) at -78 °C under a nitrogen atmosphere was added dropwise a solution of n-butyl lithium in hexanes (1.6M, 51 ml, 82.3 mmol). The reaction was stirred thus for 30 minutes then iodoethane (6.6 ml, 82.4 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature then stirred thus over the weekend.

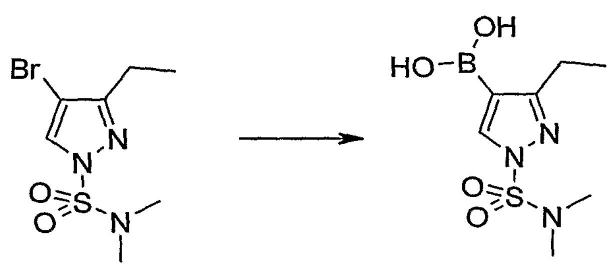
Water was then added and the solution was extracted with ethyl acetate. The separated organic liquors were washed with brine, dried ($MgSO_4$) and concentrated to furnish the title compound as a yellow/ brown oil (12.6g, 85%).

J3. 4-Bromo-3-ethyl-pyrazole-1-sulphonic acid dimethylamide



To a solution of 3-ethyl-pyrazole-1-sulphonic acid dimethylamide (12.6g, 62.1 mmol) in tetrahydrofuran at room temperature was added N-bromosuccinimide (12.7g, 68.3 mmol). After stirring for 2 hours, water was added and the product extracted into ethyl acetate. The organic layer was separated and washed with brine then dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was purified on three 40+M silica Biotage columns eluting with 5% ethyl acetate/ petrol to furnish the title compound as a pale yellow oil (7.7g, 44%).

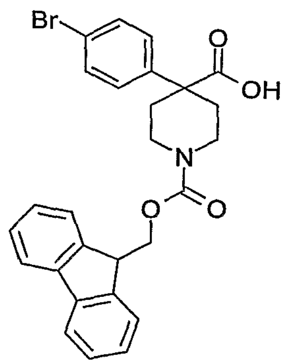
J4. 4-Bromo-3-ethyl-pyrazole-1-sulphonic acid dimethylamide



To a solution of 4-bromo-3-ethyl-pyrazole-1-sulphonic acid dimethylamide (2.4g, 8.5 mmol) and triethylborate (2.17 ml, 12.8 mmol) in anhydrous tetrahydrofuran stirred at -78 °C under a nitrogen atmosphere was added a solution of methyllithium in diethylether (1.6M, 6.9 ml, 11.1 mmol). The reaction mixture was allowed to stir, warming to room temperature overnight. The reaction mixture was then quenched with hydrochloric acid (2N), stirred for 5 minutes, then extracted into ethyl acetate (x3). The combined organic liquors were washed with brine then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified on a 40+M silica Biotage column eluting with a gradient 0-15% methanol/ dichloromethane to furnish the product as a pale coloured oil (1.2g, 57%).

PREPARATION K

4-(4-Bromo-phenyl)-piperidine-1,4-dicarboxylic acid mono-(9H-fluoren-9-ylmethyl) ester

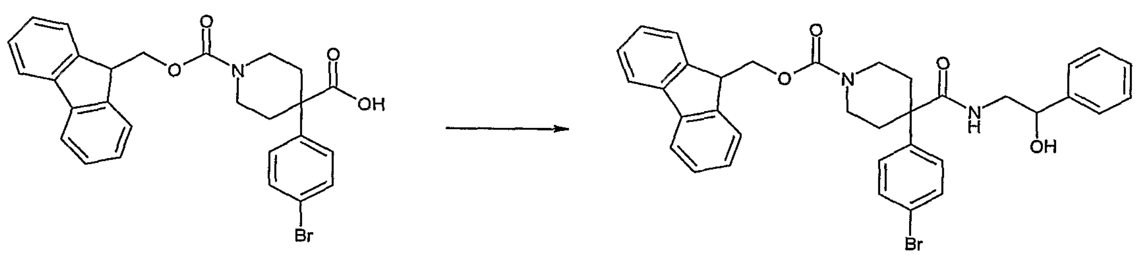


This intermediate was prepared according to the method described in Preparation A, using 4-bromophenylacetonitrile in place of 4-chlorophenylacetonitrile. However the deprotection step analogous to A3 was omitted: the BOC group was removed during the nitrile hydrolysis (step A4).

PREPARATION L

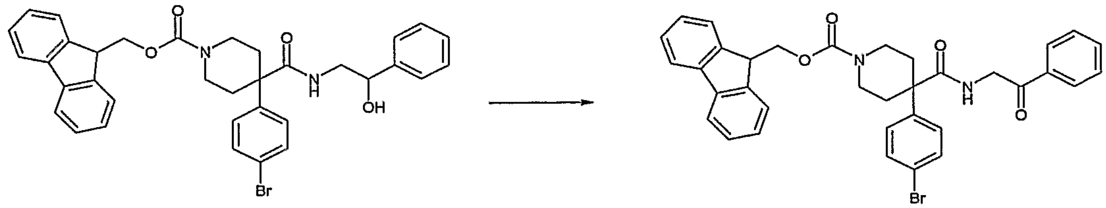
4-(4-Bromo-phenyl)-4-(5-phenyl-oxazol-2-yl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester

L1. 4-(4-Bromo-phenyl)-4-(2-hydroxy-2-phenyl-ethylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester



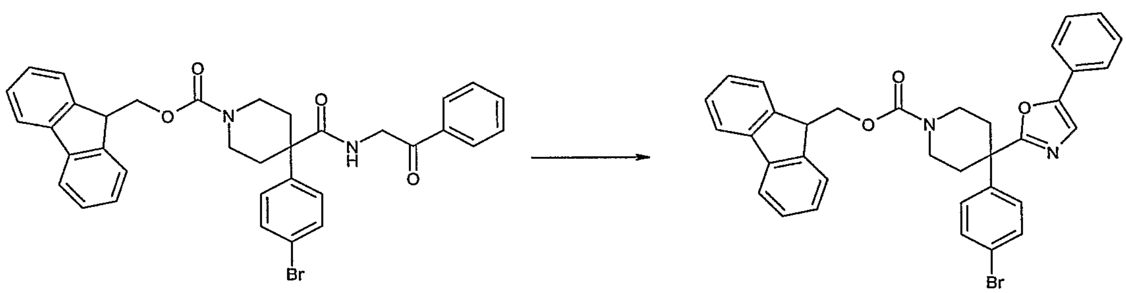
4-(4-Bromo-phenyl)-piperidine-1,4-dicarboxylic acid mono-(9H-fluoren-9-ylmethyl) ester (1g, 2.16mmol) was reacted with 2-amino-1-phenyl-ethanol (0.296g, 2.16mmol) according to Method A1 to afford the title compound as a white foam (0.487g, 36%).

L2. 4-(4-Bromo-phenyl)-4-(2-oxo-2-phenyl-ethylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester



4-(4-Bromo-phenyl)-4-(2-hydroxy-2-phenyl-ethylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (0.764g, 1.22 mmol) was dissolved in anhydrous dichloromethane (16 mL) and pyridinium chlorochromate (0.526g, 2.44 mmol) was added. The mixture was stirred for 17 hours at room temperature. The reaction mixture was then diluted with dichloromethane (50 mL) and was washed with water (2 x 50 mL). The organic was separated off, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was pre-adsorbed to silica gel and purified by flash column chromatography on silica gel, eluting with 50/ 50 petroleum ether/ ethyl acetate to afford the title compound as a white foam (0.679g, 89%).

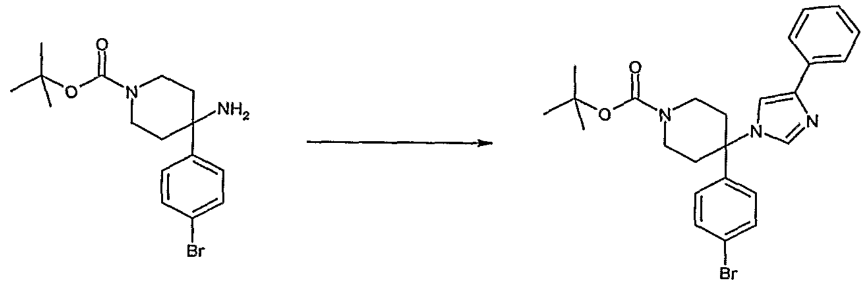
L3. 4-(4-Bromo-phenyl)-4-(5-phenyl-oxazol-2-yl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester



4-(4-Bromo-phenyl)-4-(2-oxo-2-phenyl-ethylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (0.34g, 0.545mmol) was dissolved in phosphorus oxychloride (4 mL) and the reaction mixture was heated at 110 °C for 6.5 hours. The reaction mixture was allowed to cool to room temperature and was then poured onto ice-water. The aqueous was extracted with dichloromethane (100 mL). The organic layer was separated off, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was pre-adsorbed to silica gel and purified by flash column chromatography on silica gel, eluting with 70/ 30 petroleum ether/ ethyl acetate to afford the title compound as an off-white foam (0.201g, 61%).

PREPARATION M

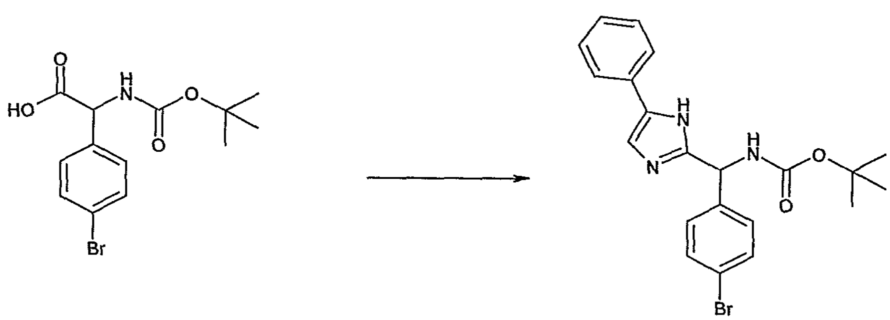
M1.4-(4-Bromo-phenyl)-4-(4-phenyl-imidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester



4-Amino-4-(4-bromo-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (0.19g, 0.535 mmol; refer to Preparation H for synthesis of this compound) and potassium carbonate (0.123g, 0.892 mmol) were mixed together and suspended in anhydrous N, N-dimethylformamide (1 mL). Glyoxylic acid (0.066g of a 50% w/w solution in water, 0.446 mmol) was dissolved in anhydrous N, N-dimethylformamide (0.5 mL) and this was added to the reaction mixture. The reaction mixture was stirred at room temperature for 3 hours and 1-(isocyano-phenyl-methanesulphonyl)-4-methyl-benzene (0.081g, 0.298 mmol) was added. The reaction mixture was then stirred at room temperature for 1 hour followed by 18 hours at 50 °C. The reaction mixture was allowed to cool and was then diluted with water (20 mL) and extracted with methyl *tert*-butyl ether (3 x 20 mL). The aqueous was further diluted with brine (20 mL) then extracted with methyl *tert*-butyl ether (2 x 20mL). The organics were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 50/ 50 petroleum ether/ ethyl acetate to afford the title compound as a yellow solid (0.027g, 19%).

PREPARATION N

N1. [(4-Bromo-phenyl)-(5-phenyl-1H-imidazol-2-yl)-methyl]-carbamic acid tert-butyl ester



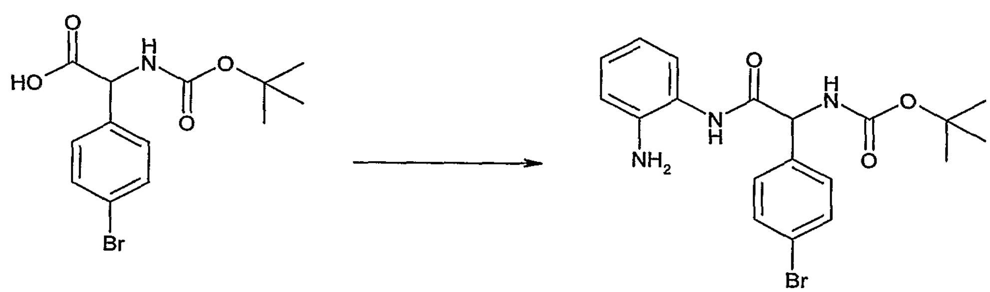
(4-Bromo-phenyl)-tert-butoxycarbonylamino-acetic acid (0.5g, 1.51 mmol; commercially available from Pharmacore) and caesium carbonate (0.247g, 0.76 mmol) were dissolved in methanol (4.6 mL) and the solution was stirred for 2 hours under nitrogen. The reaction

mixture was concentrated *in vacuo* and the residue was redissolved in N, N-dimethylformamide (6.1mL). 2-Bromo-1-phenyl-ethanone (0.301g, 1.51 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was suspended in xylenes (7.6 mL). Ammonium acetate (2.33g, 30.2 mmol) was added and the mixture was heated at 135 °C with stirring for 4 hours. The reaction was allowed to cool to room temperature and was then diluted with ethyl acetate (50 mL). The organic layer was washed with water (50 mL) followed by brine (50 mL). The organic layer was separated off, dried ($MgSO_4$) then concentrated *in vacuo*. The residue was pre-adsorbed to silica gel and purified by flash column chromatography on silica gel, eluting with 70/ 30 petroleum ether/ ethyl acetate followed by 50/ 50 petroleum ether/ ethyl acetate to afford the title compound as a yellow gum (0.171g, 26%).

PREPARATION P

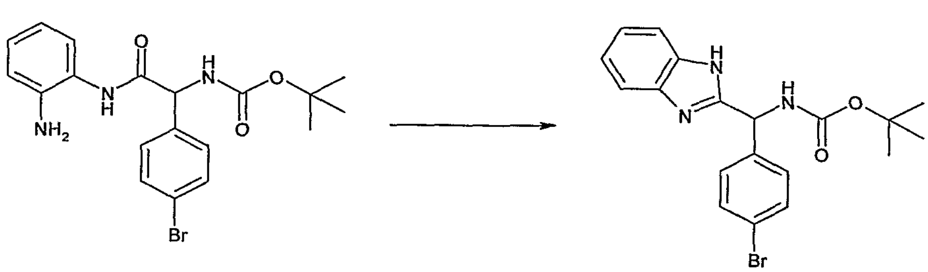
[(1H-Benzoimidazol-2-yl)-(4-bromo-phenyl)-methyl]-carbamic acid tert-butyl ester

P1. [(2-Amino-phenylcarbamoyl)-(4-bromo-phenyl)-methyl]-carbamic acid tert-butyl ester



(4-Bromo-phenyl)-tert-butoxycarbonylamino-acetic acid (1.0g, 3.03 mmol; commercially available from Pharmacore) was reacted with benzene-1,2-diamine (0.36g, 3.33 mmol) according to method A2 to afford the title compound as a cream solid (0.797g, 63%).

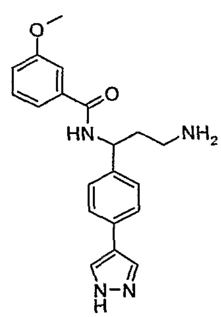
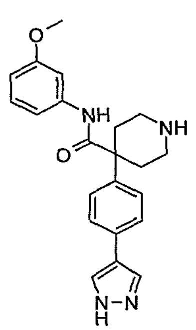
P2. [(1H-Benzoimidazol-2-yl)-(4-bromo-phenyl)-methyl]-carbamic acid tert-butyl ester

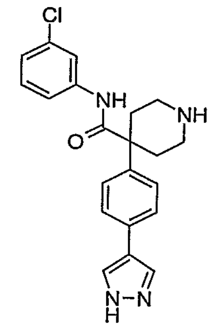
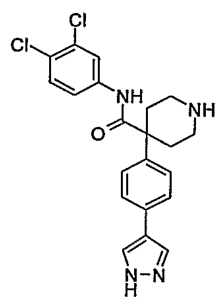
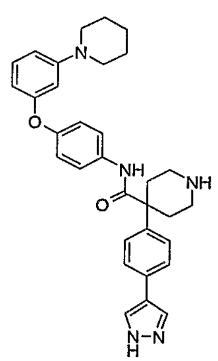


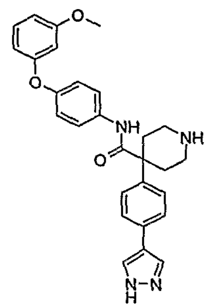
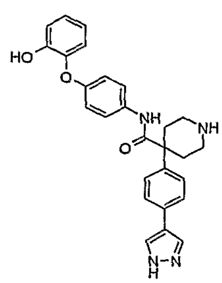
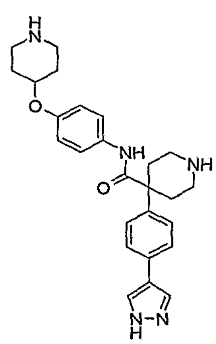
[(2-Amino-phenylcarbamoyl)-(4-bromo-phenyl)-methyl]-carbamic acid tert-butyl ester (0.4g, 0.952 mmol) was suspended in toluene (4.3 mL). Toluene-4-sulphonic acid (0.0082g, 0.043 mmol) was added and the mixture was heated at reflux for 2 hours using a Dean-Stark water trap. The reaction mixture was allowed to cool and was then diluted with ethyl acetate (50 mL). The organic layer was washed with water (50 mL) followed by aqueous 1N NaOH (50 mL). The organic layer was separated off, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a yellow solid (0.363g, 95%). The product was used without further purification.

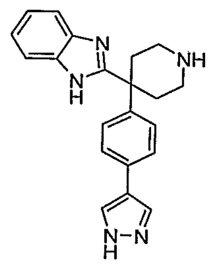
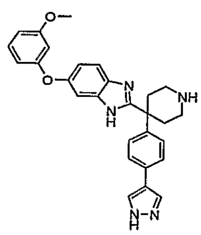
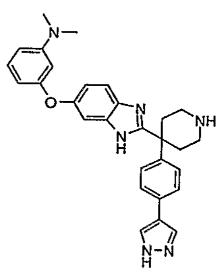
EXAMPLES

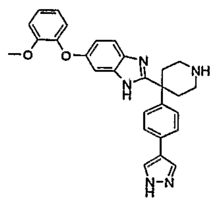
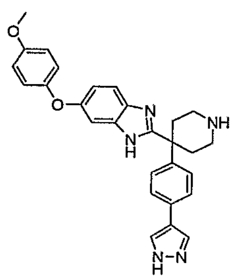
By following the methods described above, the compounds set out in the Tables below were prepared.

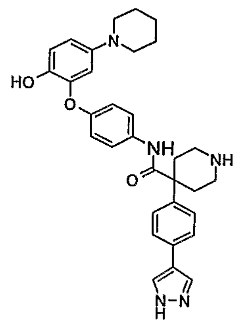
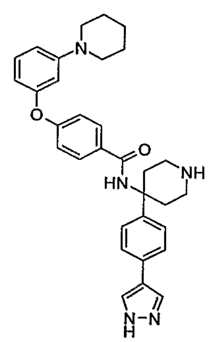
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
1		N-{3-Amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-3-methoxy-benzamide formate	1. Method A2 using Preparation C and M-Anisic acid 2. Method O1 3. Method B	^{1}H NMR (Me-d_3-OD) 7.96 (2H, s), 7.62 (2H, d), 7.46 (2H, d), 7.37-7.45 (3H, m), 7.12 (1H, d), 5.29 (1H, t), 3.85 (3H, s), 3.05-3.13 (1H, m), 2.92-3.02 (1H, m), 2.28-2.37 (2H, m)	$[M+H]^+$ 351
2		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-methoxy-phenyl)-amide acetate	1. Method A1 using Preparation A and M-Anisidine 2. Method L 3. Method B1	^{1}H NMR (Me-d_3-OD) 8.00 (2H, s), 7.68 (2H, d), 7.49 (2H, d), 7.19 (2H, m), 7.02 (1H, d), 6.70 (1H, d), 3.78 (3H, s), 3.42 (2H, m), 3.31 (2H, m), 2.81 (2H, m), 2.30 (2H, m), 2.00 (3H, s)	$[M+H]^+$ 377

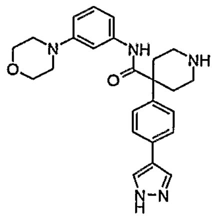
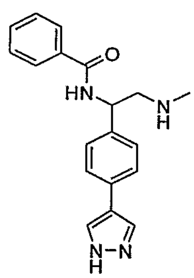
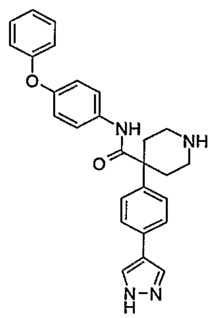
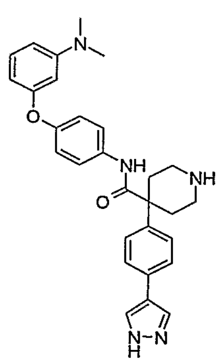
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
3		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-chloro-phenyl)-amide	1. Method A1 using Preparation A and 3-chloroaniline 2. Method L 3. Method B1	^{1}H NMR (Me-d_3-OD) 7.88 (2H, s), 7.68 (1H, s), 7.65 (2H, d), 7.45 (2H, d), 7.35 (1H, d), 7.26 (1H, t), 7.08 (1H, d), 3.10 (2H, m), 3.00 (2H, m), 2.62 (2H, m), 2.10 (2H, m)	$[M+H]^+$ 381
4		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3,4-dichloro-phenyl)-amide formate	1. Method A1 using Preparation A and 3,4-dichloroaniline 2. Method L 3. Method B1	^{1}H NMR (Me-d_3-OD) 7.99 (2H, s), 7.88 (1H, s), 7.70 (2H, d), 7.48 (2H, d), 7.40 (2H, s), 3.40 (2H, m), 3.35 (2H, m), 2.80 (2H, m), 2.35 (2H, m)	$[M+H]^+$ 415
5		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-piperidin-1-yl-phenoxy)-phenyl]-amide diacetate	1. Method D1 using 3-piperidino-phenol 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B1	^{1}H NMR (Me-d_3-OD) 8.00 (2H, s), 7.68 (2H, d), 7.50 (2H, d), 7.42 (2H, d), 7.18 (1H, t), 6.94 (2H, d), 6.70 (1H, d), 6.55 (1H, s), 6.38 (1H, d), 3.42 (2H, m), 3.34 (2H, m), 3.12 (4H, m), 2.82 (2H, d), 2.30 (2H, t), 2.00 (6H, s), 1.70 (4H, m), 1.62 (2H, m)	$[M+H]^+$ 522

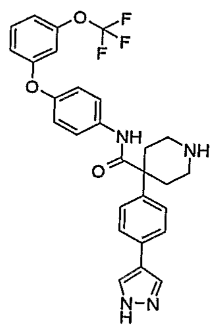
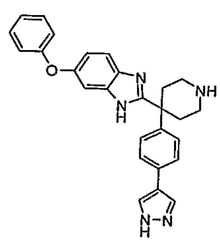
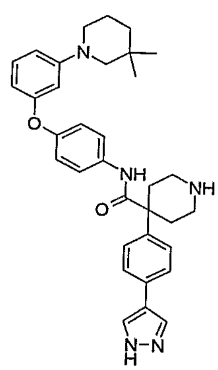
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
6		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-methoxy-phenoxy)-phenyl]-amide acetate	1. Method D1 using 3-methoxy-phenol 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B1	[1]H NMR (Me-d_3-OD) 8.05 (2H, s), 7.70 (2H, d), 7.50 (4H, m), 7.29 (1H, t), 7.01 (2H, d), 6.72 (1H, d), 6.53 (2H, m), 3.80 (3H, s), 3.49 (2H, m), 3.33 (2H, m), 2.89 (2H, d), 2.37 (2H, t), 2.00 (3H, s)	$[M+H]^+$ 469
7		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(2-hydroxy-phenoxy)-phenyl]-amide formate	1. Method D3 using catechol 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B1	[1]H NMR (Me-d_3-OD) 8.52 (1H, s)7.98 (2H, s), 7.65 (2H, d), 7.46 (2H, d), 7.36 (2H, d), 7.00 (1H, t), 6.92 (1H, d), 6.86 (2H, d), 6.79 (1H, t), 3.35 (4H, m), 2.80 (2H, d), 2.30 (2H, t)	$[M+H]^+$ 455
8		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(piperidin-4-yloxy)-phenyl]-amide tritrifluoroacetate	1. Method A1 using Preparation A and 1-boc-4-(4-amino-phenoxy)-piperidine 2. Method L 3. Method M 4. Method B1 5. Method N 6. Method M	[1]H NMR (Me-d_3-OD) 8.00 (2H, s), 7.68 (2H, d), 7.48 (2H, d), 7.38 (2H, d), 6.95 (2H, d), 3.40 (4H, m), 3.35 (2H, m), 3.22 (2H, m), 2.81 (2H, m), 2.30 (2H, m), 2.18 (2H, m), 2.02 (2H, m)	$[M+H]^+$ 446

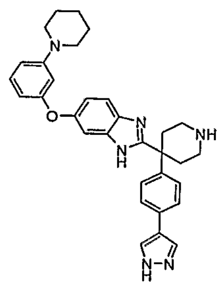
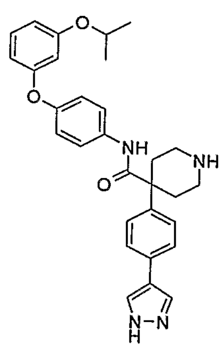
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
9		2-{4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diacetate	1. Method A1 using Preparation A and phenylene-diamine 2. Method C 3. Method L 4. Method B1	^{1}H NMR (Me-d_3-OD) 7.92 (2H, s), 7.60 (4H, m), 7.32 (2H, d), 7.25 (2H, m), 3.50 (2H, m), 3.32 (2H, m), 3.25 (2H, t), 3.01 (2H, s), 2.60 (2H, t), 2.00 (6H, s)	$[M+H]^+$ 344
10		6-(3-Methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diformate	1. Method D2 with 3-methoxy-phenol 2. Method E 3. Method A1 using Preparation A 4. Method C 5. Method L 6. Method B1	^{1}H NMR (Me-d_3-OD) 8.38 (2H, s), 7.92 (2H, s), 7.49 (3H, m), 7.31 (2H, d), 7.80 (1H, t), 7.19 (1H s), 7.00 (1H, d), 6.65 (1H, d), 6.50 (2H, m), 3.73 (3H, s), 3.45 (2H, d), 3.29 (2H, t), 3.00 (2H, d), 2.60 (2H, t)	$[M+H]^+$ 466
11		Dimethyl-[3-(2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-3H-benzoimidazol-5-yloxy)-phenyl]-amine diformate	1. Method D2 with 3-(N,N-dimethyl-amino)phenol 2. Method E 3. Method A1 using Preparation A 4. Method C 5. Method L 6. Method B1	^{1}H NMR (Me-d_3-OD) 8.52 (2H, s), 7.92 (2H, s), 7.60 (2H, d), 7.55 (1H, d), 7.32 (2H, d), 7.12 (2H, t), 7.00 (1H, d), 6.52 (1H, d), 6.41 (1H, s), 6.26 (1H, d), 3.39 (2H, m), 3.18 (2H, t), 2.92 (2H, d), 2.40 (6H, s), 2.52 (2H, t)	$[M+H]^+$ 479

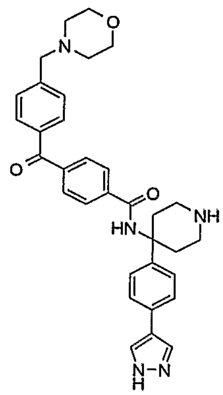
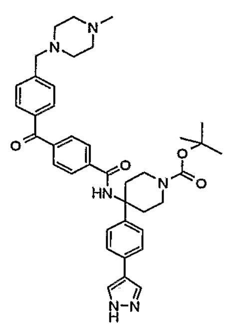
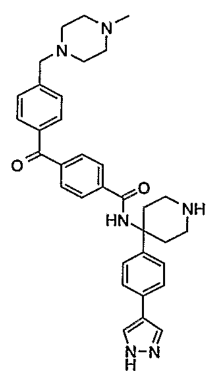
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
12		6-(2-Methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole acetate	1. Method D2 with 2-methoxy-phenol 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method C 6. Method B1	^{1}H NMR (Me-d_3-OD) 7.95 (2H, s), 7.60 (2H, d), 7.50 (1H, d), 7.32 (2H, d), 7.13 (2H, m), 6.95 (4H, m), 3.70 (3H, s), 3.42 (2H, d), 3.20 (2H, t), 2.95 (2H, d), 2.53 (2H, t), 1.99 (3H, s)	$[M+H]^+$ 466
13		6-(4-Methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diacetate	1. Method D2 with 4-methoxy-phenol 2. Method E 3. Method A1 using Preparation A 4. Method C 5. Method L 6. Method B1	^{1}H NMR (Me-d_3-OD) 7.95 (2H, s), 7.60 (2H, d), 7.52 (1H, d), 7.32 (2H, d), 7.02 (1H, s), 6.95 (4H, m), 3.79 (3H, s), 3.45 (2H, d), 3.22 (2H, t), 2.95 (2H, d), 2.55 (2H, t), 1.99 (6H, s)	$[M+H]^+$ 466

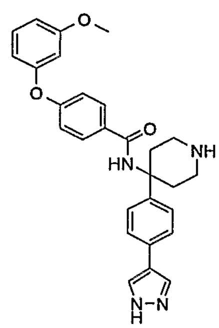
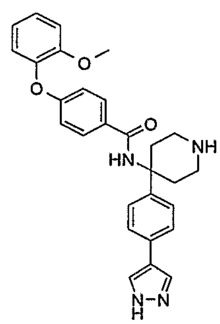
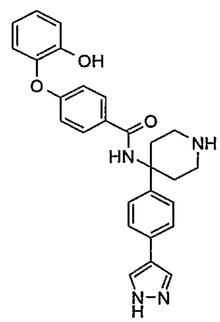
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
14		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(2-hydroxy-5-piperidin-1-yl-phenoxy)-phenyl]-amide acetate	1. Method F using piperidine and Preparation E (Note TBDMS group lost upon work-up) 2. Method D1 3. Method E 4. Method A1 using Preparation A 5. Method L 6. Method N 7. Method B1 8. Method P2	^{1}H NMR ($CDCl_3$) 8.28 (2H, s), 7.64 (2H, d), 7.42 (2H, d), 7.35 (2H, d), 7.22 (1H, d), 7.10 (1H, s), 6.98 (1H, d), 6.81 (2H, d), 3.42 (4H, m), 3.35 (2H, d), 3.25 (4H, m), 2.75 (2H, d), 2.25 (2H, t), 1.99 (3H, s), 1.90 (2H, m), 1.65 (2H, d)	$[M+H]^+$ 538
15		4-(3-Piperidin-1-yl-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide acetate	1. Method F using piperidine and 3-bromoanisole 2. Method P1 3. Method G 4. Method H 5. Method A2 using Preparation B 6. Method B1 7. Method M	^{1}H NMR (Me-d_3-OD) 7.98 (2H, s), 7.89 (2H, d), 7.60 (2H, d), 7.47 (2H, d), 7.25 (1H, t), 7.05 (2H, d), 6.82 (1H, d), 6.65 (1H, s), 6.48 (1H, d), 3.42 (4H, m), 3.15 (4H, m), 2.92 (2H, m), 2.30 (2H, m), 1.70 (4H, m), 1.62 (2H, m)	$[M+H]^+$ 522

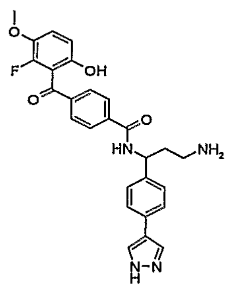
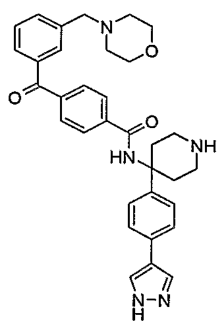
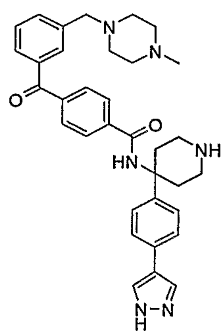
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
16		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-morpholin-4-yl-phenyl)-amide diformate	1. Method D4 using morpholine 2. Method E 3. Method A1 using preparation A 4. Method L 5. Method B1	^{1}H NMR (Me-d_3-OD) 8.45 (2H, s), 7.98 (2H, s), 7.67 (2H, d), 7.48 (2H, d), 7.19 (2H, m), 6.99 (1H, d), 6.74 (1H, d), 3.80 (4H, m), 3.42 (2H, m), 3.30 (2H, m), 2.81 (2H, d), 2.32 (2H, t)	$[M+H]^+$ 432
17		N-{2-Methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-benzamide	1. Method R 2. Method B1	^{1}H NMR (Me-d_3-OD) 7.96 (2H, s), 7.89 (2H, d), 7.62 (2H, d), 7.55 (1H, d), 7.46 (4H, br m), 5.38 (1H, m), 3.15 (1H, m), 3.04 (1H, m), 2.50 (3H, s)	$[M+H]^+$ 321
18		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4-phenoxy-phenyl)-amide acetate	1. Method D1 using phenol 2. Method Q 3. Method A1 using Preparation A 4. Method L 5. Method B1	^{1}H NMR (Me-d_3-OD) 7.86 (2H, s), 7.55 (2H, d), 7.38 (2H, d), 7.31 (2H, d), 7.22 (2H, t), 6.97 (1H, t), 6.84 (4H, m), 3.17 (2H, m), 3.09 (2H, t), 2.63 (2H, d), 2.12 (2H, t), 1.82 (3H, s)	$[M+H]^+$ 439
19		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-dimethylamino-phenoxy)-phenyl]-amide acetate	1. Method D1 using 3-Dimethyl-aminophenol 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B1	^{1}H NMR (Me-d_3-OD) 8.00 (2H, br s), 7.67 (2H, d), 7.49 (2H, d), 7.40 (2H, d), 7.14 (1H, t), 6.93 (2H, d), 6.53 (1H, d), 6.47 (1H, s), 6.25 (1H, d), 3.24 (2H, br t), 2.90 (6H, s), 2.78 (2H, br d), 2.25 (2H, br t), 1.94 (3H, s)	$[M+H]^+$ 482

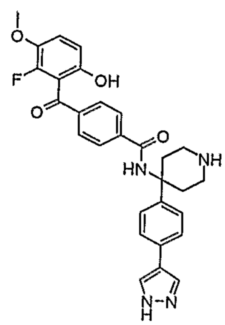
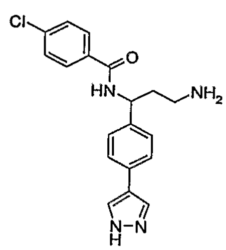
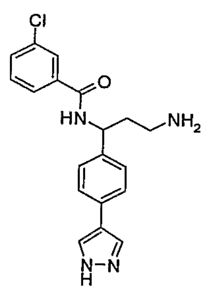
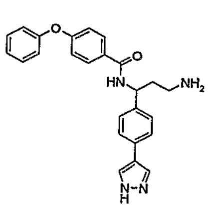
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
20		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-trifluoromethoxy-phenoxy)-phenyl]-amide acetate	1. Method using 3-(Trifluoro-methoxy)-phenol 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B1	^{1}H NMR (Me-d_3-OD) 7.98 (2H, s), 7.66 (2H, d), 7.50 (4H, m), 7.42 (1H, t), 7.03 (3H, m), 6.95 (1H, d), 6.84 (1H, s), 3.22 (2H, br t), 2.77 (2H, br d), 2.25 (2H, br t), 1.94 (3H, s)	$[M+H]^+$ 523
21		6-Phenoxy-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole	1. Method Q using 2-Nitro-5-phenoxy-phenyl-amine 2. Method A2 using Preparation A 3. Method C 4. Method L 5. Method B1	^{1}H NMR (Me-d_3-OD) 7.95 (2H, s), 7.56 (3H, d), 7.35 (4H, m), 7.15 (1H, s), 7.08 (1H, t), 6.95 (3H, m), 3.25 (2H, d), 3.03 (2H, t), 2.89 (2H, d), 2.44 (2H, t)	$[M+H]^+$ 436
22		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[3-(3,3-dimethyl-piperidin-1-yl)-phenoxy]-phenyl}-amide	1. Method D1 using 3-bromo-phenol 2. Method F using 3,3-Dimethyl-piperidine 3. Method E 4. Method A2 using Preparation B1 5. Method B1	^{1}H NMR (Me-d_3-OD) 8.0 (2H, br s), 7.67 (2H, d), 7.5 (2H, d), 7.4 (2H, d), 7.15 (1H, t), 6.94 (2H, d), 6.68 (1H, d), 6.5 (1H, s), 6.33 (1H, d), 3.25 (4H, m), 3.07 (2H, t), 2.8 (4H, m), 2.28 (2H, m), 1.7 (2H, m), 1.4 (2H, t), 1.0 (6H, s)	$[M+H]^+$ 550

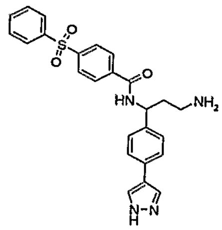
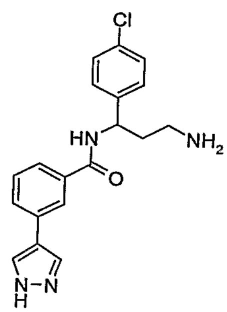
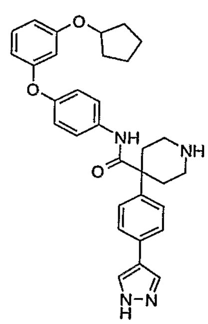
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
23		6-(3-Piperidin-1-yl-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole triacetate	1. Method F using 3-bromo-anisole and piperidine 2. Method P1 3. Method D2 4. Method E 5. Method A using Preparation A 6. Method C 7. Method L 8. Method B1	^{1}H NMR (Me-d_3-OD) 7.95 (2H, s), 7.6 (2H, d), 7.56 (1H, d), 7.35 (2H, d), 7.15 (2H, m), 7.0 (1H, d), 6.72 (1H, d), 6.6 (1H, br s), 6.4 (1H, d), 3.24 (2H, br t), 3.12 (4H, m), 2.98 (2H, br d), 2.57 (2H, br t), 1.98 (9H, s), 1.7 (4H, m), 1.6 (2H, m)	$[M+H]^+$ 519
24		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-isopropoxy-phenoxy)-phenyl]-amide acetate	1. Method I using 2-propanol 2. Method K 3. Method D1 4. Method E 5. Method A1 using Preparation A 6. Method L 7. Method B1	^{1}H NMR (Me-d_3-OD) 8.0 (2H, s), 7.67 (2H, d), 7.49 (2H, d), 7.45 (2H, d), 7.2 (1H, t), 6.69 (2H, d), 6.65 (1H, d), 6.5 (2H, d), 4.53 (1H, m), 3.4 (2H, m), 3.28 (2H, m), 2.7 (2H, br d), 2.3 (2H, br t), 1.95 (3H, s), 1.28 (6H, d)	$[M+H]^+$ 497

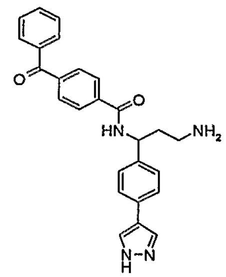
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
25		4-(4-Morpholin-4-ylmethyl-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method J using 4-(4-Morpholin-4-ylmethyl-benzoyl)-benzoic acid ethyl ester 2. Method A2 using Preparation B 3. Method B1 4. Method M	^{1}H NMR (Me-d_3-OD) 7.95 (2H, d), 7.94 (2H, s), 7.86 (2H, d), 7.79 (2H, d), 7.58 (4H, t), 7.50 (2H, d), 3.75-3.68 (4H, m), 3.65 (2H, s), 3.14-3.01 (4H, m), 2.70-2.61 (2H, m), 2.54-2.46 (4H, m), 2.17-2.07 (2H, m)	$[M+H]^+$ 550
26		4-{4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzoyl]-benzoylamino}-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester	1. Method J using 4-[4-(4-Methyl-piperazin-1-yl-methyl)-benzoyl]-benzoic acid ethyl ester 2. Method A2 using Preparation B 3. Method B1	^{1}H NMR (Me-d_3-OD) 7.96 (2H, d), 7.94 (2H, s), 7.85 (2H, d), 7.78 (2H, d), 7.55 (4H, q), 7.48 (2H, d), 4.05 (2H, d), 3.66 (2H, s), 3.37-3.21 (2H, m,) 2.72-2.39 (10H, m), 2.30 (3H, s), 2.10-1.99 (2H, m), 1.52 (9H, s)	$[M+H]^+$ 663
27		4-[4-(4-Methyl-piperazin-1ylmethyl)-benzoyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method J using 4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzoyl]-benzoic acid ethyl ester 2. Method A2 using Preparation B 3. Method B1 4. Method M	^{1}H NMR (Me-d_3-OD) 7.96 (2H, d), 7.94 (2H, s), 7.86 (2H, d), 7.79 (2H, d), 7.55 (4H, d), 7.49 (2H, d), 3.65 (2H, s), 3.12-3.00 (4H, m), 2.69-2.41 (10H, m), 2.30 (3H, s), 2.16-2.06 (2H, m)	$[M+H]^+$ 563

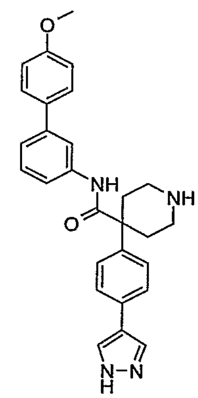
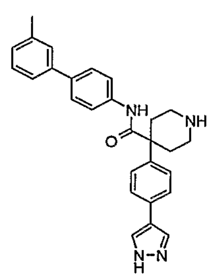
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
28		4-(3-Methoxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method G using 3-Methoxy-phenol 2. Method H 3. Method A2 using Preparation B 4. Method B1 5. Method M	^{1}H NMR (DMSO-d_6) 7.94 (2H, s), 7.85 (2H, d), 7.56 (2H, d), 7.47 (2H, d), 7.31 (1H, t), 7.05 (2H, d), 6.78 (1H, br d), 6.65-6.62 (2H, m), 3.79 (3H, s), 3.09-2.98 (4H, m), 2.67-2.58 (2H, m), 2.13-2.04 (2H, m)	$[M+H]^+$ 469
29		4-(2-Methoxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method G using 2-Methoxy phenol 2. Method H 3. Method A2 using Preparation B 4. Method B1 5. Method M	^{1}H NMR (DMSO-d_6) 12.89 (1H, br s), 8.08 (1H, s), 7.99 (2H, br s), 7.80 (2H, d), 7.51 (2H, d), 7.36 (2H, d), 7.26 (1H, t), 7.21 (1H, d), 7.12 (1H, d), 7.01 (1H, t), 6.86 (2H, d), 3.74 (3H, s), 2.89-2.77 (4H, m), 2.53-2.44 (2H, m), 1.85-1.74 (2H, m)	$[M+H]^+$ 469
30		4-(2-Hydroxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method G using 2-Methoxy phenol 2. Method H 3. Method A2 using Preparation B 4. Method B1 5. Method M 6. Method P2	^{1}H NMR (DMSO-d_6) 8.05 (1H, s) 7.97 (2H, br s), 7.81 (2H, d), 7.50 (2H, d), 7.36 (2H, d), 7.09 (1H, t), 7.01 (2H, t), 6.90-6.82 (3H, m), 2.88-2.77 (4H, m), 2.53-2.45 (2H, m), 1.84-1.73 (2H, m)	$[M+H]^+$ 455

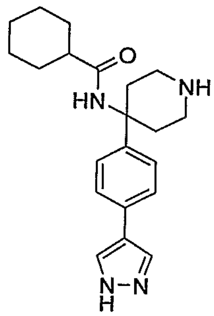
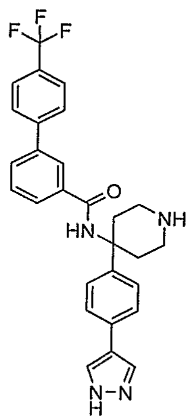
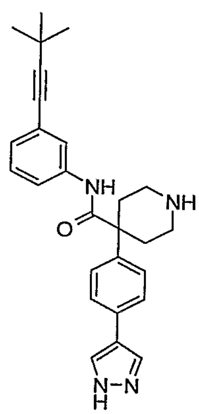
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
31		N-{3-Amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-benzamide	1. Method M using Preparation C 2. Method A2 using Preparation D 3. Method B1 4. Method O2 5. Method M	^{1}H NMR (Me-d_3-OD) 8.25 (2H, s), 7.97 (2H, d), 7.92 (2H, d), 7.69 (2H, d), 7.54 (2H, d), 7.15 (1H, t), 6.70 (1H, d), 5.29 (1H, m), 3.85 (3H, s), 3.13 (1H, m), 3.00 (1H, m), 2.35 (2H, br m), 2.00 (3H, s)	$[M+H]^+$ 489
32		4-(3-Morpholin-4-ylmethyl-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method J using 4-(3-Morpholin-4-ylmethyl-benzoyl)-benzoic acid ethyl ester 2. Method A2 using Preparation B 3. Method B1 4. Method M	^{1}H NMR (Me-d_3-OD) 8.81 (1H, s), 8.10 (2H, s), 8.05 (3H, d), 7.94 (3H, m), 7.89 (1H, d), 7.72 (1H, t), 7.65 (2H, d), 7.55 (2H, d), 4.50 (2H, s), 4.07 (2H, br d), 3.80 (2H, br t), 3.45 (4H, m), 3.26 (2H, m), 2.59 (2H, br d), 2.38 (2H, m), 2.0 (3H, s)	$[M+H]^+$ 550
33		4-[3-(4-Methyl-piperazin-1-ylmethyl)-benzoyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method J using 4-[3-(4-Methyl-piperazin-1-ylmethyl)-benzoyl]-benzoic acid ethyl ester 2. Method A2 using Preparation B 3. Method B1 4. Method M	^{1}H NMR (Me-d_3-OD) 8.50 (2H, s), 7.98 (4H, m), 7.88 (2H, d), 7.80 (1H, s), 7.72 (1H, d), 7.68 (1H, d), 7.63 (2H, d), 7.52 (3H, m), 3.66 (2H, s), 3.44 (4H, m), 2.96 (2H, br d), 2.80-2.50 (8H, m), 2.45 (3H, s), 2.35 (2H, m)	$[M+H]^+$ 563

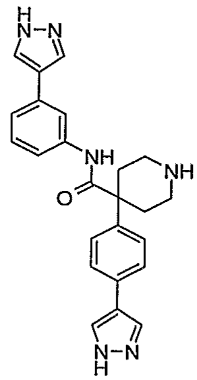
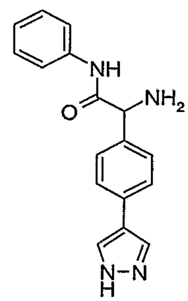
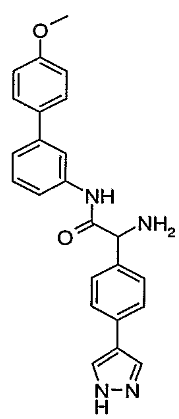
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
34		4-(2-Fluoro-6-hydroxy-3-methoxy-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method A2 using Preparation B and Preparation D 2. Method B1 3. Method M	^{1}H NMR (DMSO-d_6) 8.00 (2H, br m), 7.94 (2H, d), 7.84 (2H, d), 7.53 (2H, d), 7.37 (2H, d), 7.18 (1H, t), 6.75 (1H, d), 3.80 (3H, s), 2.90 (4H, m), 1.89 (6H, s)	$[M+H]^+$ 515
35		N-{3-Amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-4-chloro-benzamide	1. Method B1 using Preparation C 2. Method M 3. Method A2 using 4-chlorobenzoic acid 4. Method O1	^{1}H NMR (Me-d_3-OD) 8.50(1H, s), 7.96 (2H, s), 7.85 (2H, d), 7.50 (2H, d), 7.48 (2H, d), 5.36 (1H, t), 3.08 (1H, m), 2.96 (1H, m), 2.3 (2H, t)	$[M+H]^+$ 355
36		N-{3-Amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-3-chloro-benzamide	1. Method B1 using Preparation C 2. Method M 3. Method A2 using 3-chlorobenzoic acid 4. Method O1	^{1}H NMR (Me-d_3-OD) 7.96 (2H, s), 7.85 (1H, s), 7.80 (1H, d), 7.58 (3H, dd), 7.45 (3H, dd) 5.23 (1H, t), 2.85 (2H, m), 2.14 (2H, t)	$[M+H]^+$ 355
37		N-{3-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-4-phenoxy-benzamide	1. Method B1 using Preparation C 2. Method M 3. Method A2 using 4-phenoxy-benzoic acid 4. Method O1	^{1}H NMR (Me-d_3-OD) 8.60(1H, s), 7.96 (2H, br s), 7.95 (2H, d), 7.62 (2H, d), 7.43 (4H, dd), 7.23 (1H, t), 7.06 (4H, dd), 5.29 (1H, t), 3.08 (1H, m), 2.96 (1H, m), 2.3 (2H, m)	$[M+H]^+$ 413

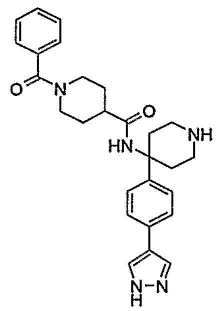
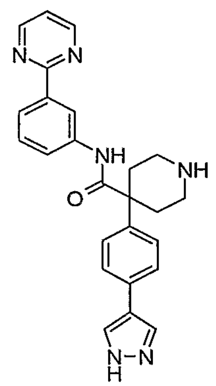
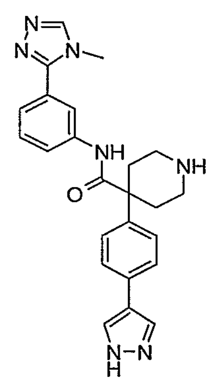
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
38		N-{3-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-4-benzene sulphonyl-benzamide	1. Method B1 using Preparation C 2. Method M 3. Method A2 using 4-benzene-sulphonyl-benzoic acid 4. Method O1	^{1}H NMR (Me-d_3-OD) 8.08(2H, d), 7.98 (4H, dd), 7.94 (2H, d), 7.68 (1H, d), 7.62 (4H, dd), 7.41 (2H, d), 5.29 (1H, t), 2.85 (2H, m), 2.20 (2H, m)	$[M+H]^+$ 461
39		N-[3-amino-1-(4-chloro-phenyl)-propyl]-3-(1H-pyrazol-4-yl)-benzamide	1. Method M using Preparation C 2. Method A3 using 3-bromobenzoyl chloride 3. Method B 4. Method O1	^{1}H NMR (Me-d_3-OD) 8.58(1H, s), 8.50 (3H, d)7.81 (1H, d), 7.72 (1H, d), 7.48 (3H, m), 7.39 (2H, d), 5.29 (1H, t), 2.95 (2H, m), 2.25 (2H, m)	$[M+H]^+$ 355
40		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-cyclopentyloxy-phenoxy)-phenyl]-amide formate	1. Method I using cyclopentanol 2. Method K 3. Method D1 4. Method E 5. Method A1 using Preparation A 6. Method L 7. Method B	^{1}H NMR (Me-d_3-OD) 8.50 (1H, s), 8.00 (2H, s), 7.69 (2H, d), 7.49 (2H, d), 7.42 (2H, d), 7.20 (1H, t), 6.95 (2H, d), 6.62 (1H, d), 6.45 (2H, m), 4.72 (1H, m), 3.42 (2H, m), 3.30 (2H, m), 2.81 (2H, d), 2.31 (2H, t), 1.90 (2H, m), 1.79 (4H, m), 1.63 (2H, m)	$[M+H]^+$ 523

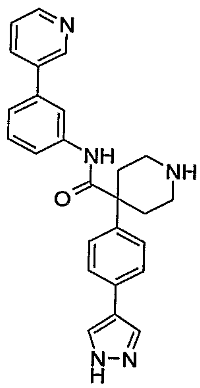
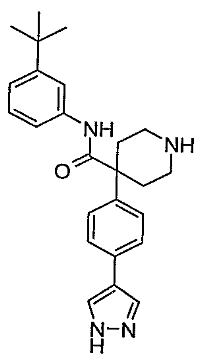
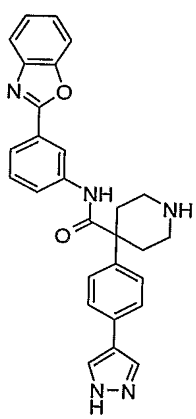
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
41		N-[{-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-benzoyl-benzamide	1. Method B1 using Preparation C 2. Method M 3. Method A2 using 4-benzoyl-benzoic acid 4. Method O1	^{1}H NMR (Me-d_3-OD) 8.03(4H, dd), 7.88(2H,d), 7.80(2H, d), 7.57 (3H, m), 7.56 (2H, t), 7.49 (2H, d), 5.29 (1H, br t), 3.12 (1H, m), 3.01 (1H, m), 2.33 (2H, m)	$[M+H]^+$ 425

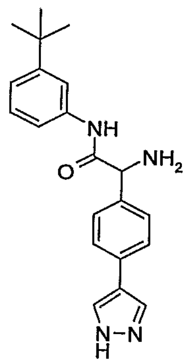
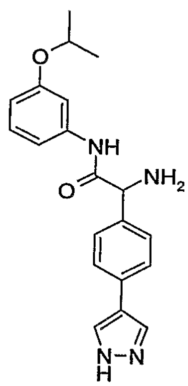
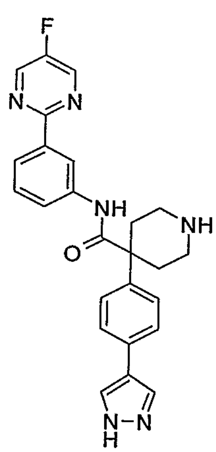
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
42		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methoxy-biphenyl-3-yl)-amide acetate	1. Method A1 using Preparation A and 4'-methoxy-biphenyl-3-ylamine 2. Method L 3. Method B	^{1}H NMR (Me-d_3-OD) 7.99 (2H, s), 7.71 (1H, s), 7.68 (2H, d), 7.52 (2H, d), 7.50 (2H, d), 7.41 (1H, m), 7.34 (2H, m), 6.98 (2H, d), 3.82 (3H, s), 3.41 (2H, m), 3.33 (partially obscured, 2H, m), 2.82 (2H, d), 2.30 (2H, m), 1.99 (3H, s)	$[M+H]^+$ 453.00
43		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3'-methyl-biphenyl-4-yl)-amide	1. Method A1 using Preparation A and 3'-Methyl-biphenyl-4-ylamine 2. Method L 3. Method B	^{1}H NMR (DMSO-d_6) 8.00 (2H, br s), 7.68 (2H, d), 7.57 (4H, t), 7.40 (4H, t), 7.30 (1H, t), 7.13 (1H, d), 2.88 (2H, br d), 2.72 (2H, br t), 2.55 (partially obscured, 2H, m), 2.35 (3H, s), 2.86 (2H, m)	$[M+H]^+$ 437.34

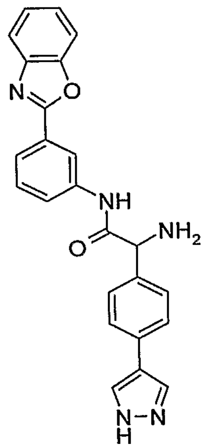
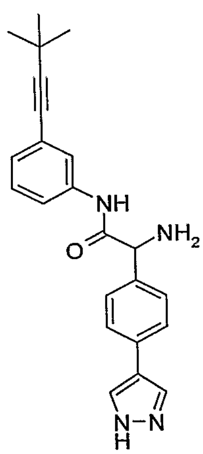
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
44		Cyclohexanecarboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate	1. Method A2 using Preparation B and Cyclohexane-carboxylic acid 2. Method M 3. Method B	^{1}H NMR (Me-d_3-OD) 7.96 (2H, s), 7.59 (2H, d), 7.40 (2H, d), 3.37 (partially obscured, 2H, m), 3.25 (2H, t), 2.72 (2H, d), 2.39 (1H, m), 2.24 (2H, m), 1.83 (4H, m), 1.72 (1H, m), 1.40 (4H, m).	$[M+H]^+$ 353.34
45		4'-Trifluoromethyl-biphenyl-3-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate	1. Method A2 using Preparation B and 4'-Trifluoromethyl-biphenyl-3-carboxylic acid 2. Method M 3. Method B	^{1}H NMR (Me-d_3-OD) 8.16 (1H, s), 7.98 (2H, s), 7.90 (4H, m), 7.79 (2H, d), 7.63 (3H, m), 7.51 (2H, d), 3.39 (4H, d), 2.92 (2H, d), 2.30 (2H, m), 1.94 (3H, s).	$[M+H]^+$ 491.25
46		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide	1. Method S using 3-iodoaniline and 3,3-dimethyl-1-butyne 2. Method A1 using Preparation A 3. Method L 4. Method B	^{1}H NMR (Me-d_3-OD) 7.97 (2H, s), 7.65 (2H, d), 7.54 (1H, m), 7.48 (2H, d), 7.33 (1H, d), 7.20 (1H, t), 7.08 (1H, d), 3.17 (2H, m), 3.08 (2H, m), 2.66 (2H, br d), 2.17 (2H, m), 1.32 (9H, s).	$[M+H]^+$ 427.31

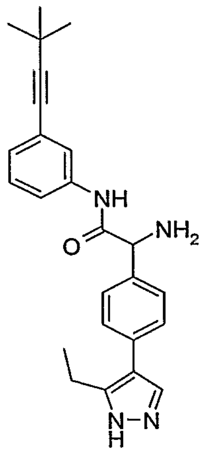
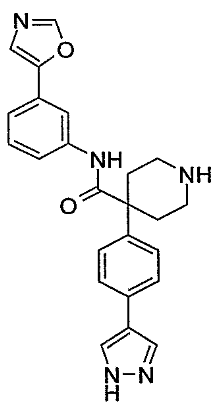
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
47		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(1H-pyrazol-4-yl)-phenyl]-amide	1. Method A1 using Preparation A and 3-iodoaniline 2. Method L 3. Method B	^{1}H NMR (Me-d_3-OD) 7.95 (4H, br d), 7.70 (1H, s), 7.65 (2H, d), 7.49 (2H, d), 7.34 (3H, m), 3.28 (2H, m), 3.19 (2H, m), 2.76 (2H, br d), 2.24 (2H, m).	$[M+H]^+$ 413.24
48		2-Amino-N-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide acetate	1. Method A2 using aniline and (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 2. Method M 3. Method B2	^{1}H NMR (Me-d_3-OD) 7.99 (2H, s), 7.67 (2H, d), 7.56 (4H, m), 7.33 (2H, t), 7.12 (1H, t), 4.84 (1H, s), 1.96 (3H, s).	$[M+H]^+$ 293.23
49		2-Amino-N-(4'-methoxy-biphenyl-3-yl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide acetate	1. Method A2 using 4'-methoxy-biphenyl-3-ylamine and (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 2. Method M 3. Method B2	^{1}H NMR (Me-d_3-OD) 7.99 (2H, s), 7.82 (1H, s), 7.66 (2H, d), 7.55 (4H, d), 7.51 (1H, m), 7.35 (2H, m), 7.00 (2H, d), 4.77 (1H, s), 3.85 (3H, s), 1.96 (3H, s).	$[M+H]^+$ 399.25

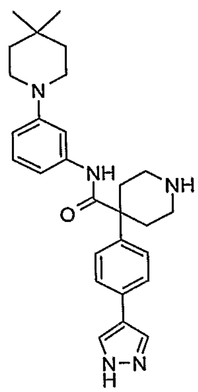
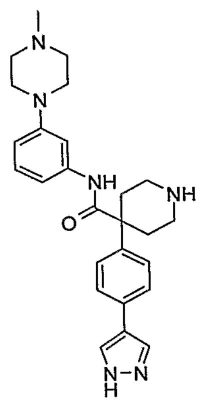
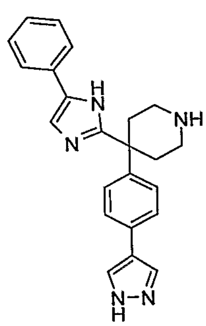
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
50		1-Benzoyl-piperidine-4-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate	1. Method A2 using Preparation B and 1-benzoyl-piperidine-4-carboxylic acid 2. Method M 3. Method B	^{1}H NMR (Me-d_3-OD) 7.95 (2H, s), 7.59 (2H, d), 7.48 (3H, m), 7.39 (4H, m), 4.67 (1H, br s), 3.79 (1H, br s), 3.22 (3H, m), 2.96 (1H, br s), 2.70 (3H, m), 2.20 (2H, m), 1.95 (6H, m), 1.70 (3H, br m).	$[M+H]^+$ 458.31
51		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-pyrimidin-2-yl-phenyl)-amide diacetate	1. Method B2 using 2-bromo-pyrimidine and 3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2. Method A1 using Preparation K 3. Method L 4. Method B2	^{1}H NMR (Me-d_3-OD) 8.84 (2H, d), 8.50 (1H, m), 8.18 (1H, d), 7.99 (2H, s), 7.69 (3H, m), 7.52 (2H, d), 7.46 (1H, t), 7.39 (1H, t), 3.40 (partially obscured, 4H, m), 2.85 (2H, d), 2.33 (2H, m), 1.96 (6H, s).	$[M+H]^+$ 425.23
52		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-amide diacetate	1. Method A1 using Preparation K and 3-(4-methyl-4H-1,2,4-triazol-3-yl)aniline 2. Method L 3. Method B2	^{1}H NMR (Me-d_3-OD) 8.56 (1H, s), 7.97 (2H, s), 7.95 (1H, m), 7.68 (3H, m), 7.50 (4H, m), 3.82 (3H, s), 3.70 (0.5H, t), 3.58 (0.5H, t), 3.40 (2H, m), 3.30 (partially obscured, 2H, m), 2.81 (2H, d), 2.30 (2H, m), 1.94 (6H, s).	$[M+H]^+$ 428.26

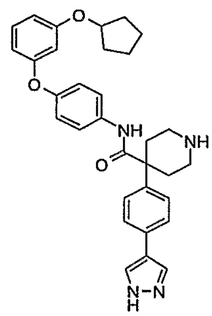
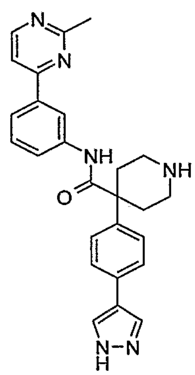
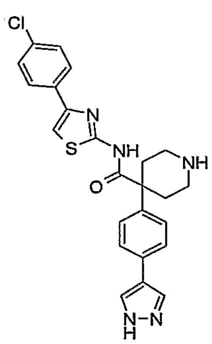
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
53		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-pyridin-3-yl-phenyl)-amide diacetate	1. Method B2 using 3-iodoaniline and 3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine 2. Method A1 using Preparation K 3. Method L 4. Method B2	^{1}H NMR (Me-d_3-OD) 8.79 (1H, d), 8.55 (1H, dd), 8.08 (1H, m), 7.98 (2H, s), 7.85 (1H, t), 7.69 (2H, d), 7.53 (4H, m), 7.45 (2H, m), 3.42 (2H, m), 3.35 (partially obscured, 2H, m), 2.85 (2H, d), 2.33 (2H, m), 1.96 (6H, s).	$[M+H]^+$ 424.20
54		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-tert-butyl-phenyl)-amide acetate	1. Method A1 using Preparation K and 3-(tert-butyl)aniline 2. Method L 3. Method B2	^{1}H NMR (Me-d_3-OD) 7.99 (2H, s), 7.66 (2H, d), 7.50 (3H, m), 7.35 (1H, d), 7.24 (1H, t), 7.19 (1H, m), 3.38 (partially obscured, 2H, m), 3.28 (2H, m), 2.80 (2H, d), 2.29 (2H, m), 1.94 (3H, s), 1.30 (9H, s).	$[M+H]^+$ 403.24
55		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-benzooxazol-2-yl-phenyl)-amide diacetate	1. Method A1 using Preparation K and 3-benzooxazol-2-yl-phenylamine 2. Method L 3. Method B2	^{1}H NMR (Me-d_3-OD) 8.48 (1H, t), 8.00 (3H, m), 7.76 (1H, dd), 7.70 (4H, m), 7.55 (3H, m), 7.45 (2H, m), 3.44 (2H, m), 3.38 (partially obscured, 2H, m), 2.87 (2H, d), 2.33 (2H, m), 1.96 (6H, s).	$[M+H]^+$ 464.24

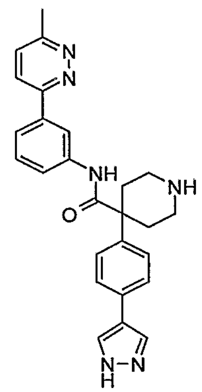
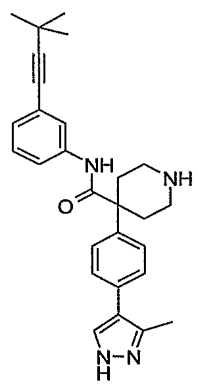
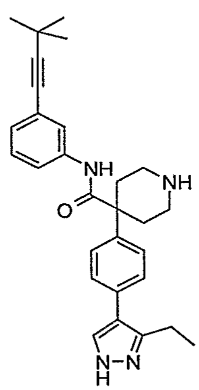
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
56		2-Amino-N-(3-tert-butyl-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride	1. Method A2 using and 3-(tert-butyl)aniline and (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 2. Method B2 3. Method M	^{1}H NMR (Me-d_3-OD) 8.37 (2H, s), 7.81 (2H, d), 7.66 (2H, d), 7.58 (1H, s), 7.45 (2H, d), 7.28 (1H, t), 7.20 (1H, d), 5.13 (1H, s), 1.30 (9H, s)	$[M+H]^+$ 349.16
57		2-Amino-N-(3-isopropoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride	1. Method A2 using and 3-isopropoxy-aniline and (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 2. Method B2 3. Method M	^{1}H NMR (Me-d_3-OD) 8.35 (2H, s), 7.80 (2H, d), 7.65 (2H, d), 7.26 (1H, m), 7.20 (1H, t), 7.06 (1H, d), 6.70 (1H, d), 5.12 (1H, s), 4.57 (1H, m), 1.30 (6H, d).	$[M+H]^+$ 351.17
58		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(5-fluoro-pyrimidin-2-yl)-phenyl]-amide diacetate	1. Method B2 using 2-chloro-5-fluoro-pyrimidine and 3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2. Method A1 using Preparation K 3. Method L 4. Method B2	^{1}H NMR (Me-d_3-OD) 8.78 (2H, s), 8.50 (1H, s), 8.17 (1H, d), 7.99 (2H, s), 7.69 (2H, d), 7.65 (1H, d), 7.51 (2H, d), 7.45 (1H, t), 3.47 (2H, m), 3.38 (partially obscured, 2H, m), 2.88 (2H, d), 2.33 (2H, m), 1.98 (6H, s).	$[M+H]^+$ 443.19

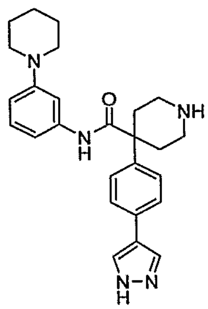
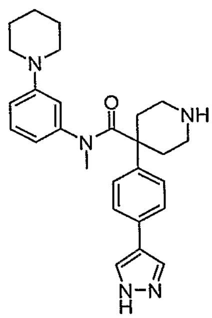
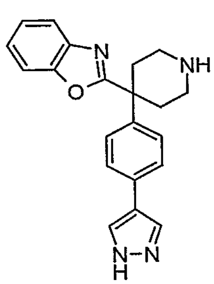
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
59		2-Amino-N-(3-benzooxazol-2-yl-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride	1. Method A2 using 3-benzooxazol-2-yl-phenylamine and (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 2. Method B2 3. Method M	^{1}H NMR (Me-d_3-OD) 8.60 (1H, s), 8.29 (2H, s), 8.03 (1H, d), 7.82 (2H, d), 7.77 (2H, d), 7.69 (3H, m), 7.57 (1H, t), 7.45 (2H, m), 5.19 (1H, s).	$[M+H]^+$ 410.13
60		2-Amino-N-[3-(3,3-dimethyl-but-1-ynyl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide	1. Method S using 3-iodoaniline and 3,3-dimethyl-1-butyne 2. Method A2 using (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 3. Method B2 4. Method M	^{1}H NMR (Me-d_3-OD) 7.97 (2H, br s), 7.62 (3H, m), 7.50 (2H, d), 7.46 (1H, d), 7.24 (1H, t), 7.08 (1H, d), 4.60 (1H, s), 1.33 (9H, s).	$[M+H]^+$ 373.22

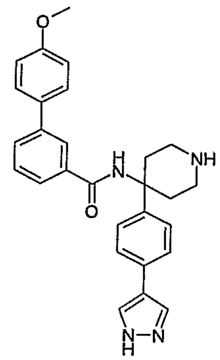
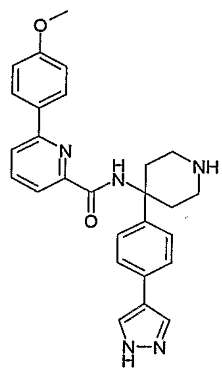
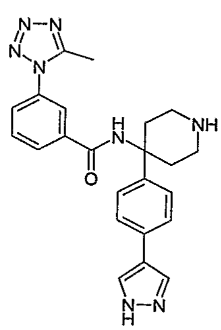
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
61		2-Amino-N-[3-(3,3-dimethyl-but-1-ynyl)-phenyl]-2-[4-(5-ethyl-1H-pyrazol-4-yl)-phenyl]-acetamide	1. Method S using 3-iodoaniline and 3,3-dimethyl-1-butyne 2. Method A2 using (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 3. Method B2 using Preparation I 4. Method T	^{1}H NMR (Me-d_3-OD) 7.65 (2H, s), 7.53 (2H, d), 7.45 (3H, m), 7.25 (1H, t), 7.08 (1H, d), 4.62 (1H, s), 2.85 (2H, q), 1.33 (9H, s), 1.24 (3H, t).	$[M+H]^+$ 401.25
62		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-oxazol-5-yl-phenyl)-amide diacetate	1. Method A1 using Preparation K and 3-(1,3-oxazol-5-yl)aniline 2. Method L 3. Method B2	^{1}H NMR (Me-d_3-OD) 8.25 (1H, s), 8.00 (2H, s), 7.95 (1H, t), 7.65 (2H, d), 7.50 (5H, m), 7.40 (1H, dd), 3.42 (2H, m), 3.30 (2H, m), 2.83 (2H, d), 2.31 (2H, m), 1.95 (6H, s)	$[M+H]^+$ 414

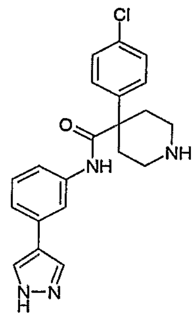
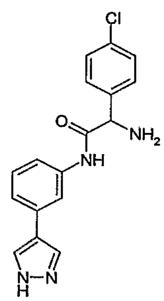
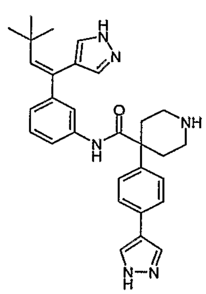
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
63		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4,4-dimethyl-piperidin-1-yl)-phenyl]-amide	1. Method F using Preparation F and 1-bromo-3-nitrobenzene 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B	^{1}H NMR (Me-d_3-OD) 7.97 (2H, s), 7.62 (2H, d), 7.48 (2H, d), 7.18-7.12 (2H, m), 6.96-6.91 (1H, m), 6.78-6.72 (1H, m), 3.16-2.96 (8H, m), 2.68-2.59 (2H, m), 2.16-2.06 (2H, m), 1.55-1.48 (4H, m), 0.99 (6H, s)	[M+H]$^+$ 458
64		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4-methyl-piperazin-1-yl)-phenyl]-amide	1. Method F using 1-methyl-piperazine and 1-bromo-3-nitrobenzene 2. Method E 3. Method A1 using Preparation A 4. Method L 5. Method B	^{1}H NMR (DMSO-*d6*) 12.91 (br s), 8.91 (1H, s), 8.01 (2H, br s), 7.58 (2H, d), 7.38 (2H, d), 7.19 (1H, br s), 7.15-7.04 (2H, m), 6.61 (1H, br d), 3.10-3.02 (4H, m), 2.90-2.79 (2H, m), 2.73-2.63 (2H, m), 2.56-2.47 (2H, m), 2.46-2.39 (4H, m), 2.21 (3H, s), 1.87-1.75 (2H, m)	[M+H]$^+$ 445
65		4-(5-Phenyl-1H-imidazol-2-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine	1. Method U using Preparation K and 2-bromo-acetophenone 2. Method B	^{1}H NMR (Me-*d3*-OD) 8.25 (2H, br s), 7.91 (1H, s), 7.83-7.75 (4H, m), 7.58-7.47 (5H, m), 3.46-3.36 (4H, m), 3.07-2.92 (4H, m)	[M+H]$^+$ 370

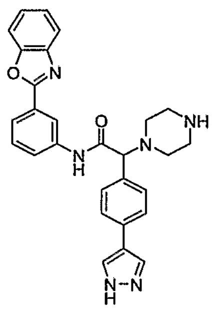
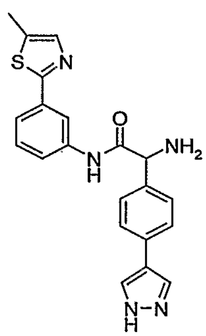
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
66		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-cyclopentyloxy-phenoxy)-phenyl]-amide formate	1. Method I using cyclopentyl alcohol 2. Method K 3. Method D1 4. Method E 5. Method A1 using Preparation A 6. Method L 7. Method B	^{1}H NMR (Me-d_3-OD) 8.50 (1H, s), 8.00 (2H, s), 7.69 (2H, d), 7.49 (2H, d), 7.42 (2H, d), 7.20 (1H, t), 6.95 (2H, d), 6.62 (1H, d), 6.45 (2H, m), 4.72 (1H, m), 3.42 (2H, m), 3.30 (2H, m), 2.81 (2H, d), 2.31 (2H, t), 1.90 (2H, m), 1.79 (4H, m), 1.63 (2H, m)	$[M+H]^+$ 523
67		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(2-methyl-pyrimidin-4-yl)-phenyl]-amide trihydrochloride	1. Method A1 using 3-(2-methyl-pyrimidin-4-yl)aniline and Preparation K 2. Method L 3. Method B	^{1}H NMR (DMSO-d_6) 9.82 (1H, s), 9.52 (1H, bs), 9.40 (1H, bs), 8.80 (1H, d), 8.48 (1H, s), 8.09 (2H, s), 8.41 (2H, m), 7.86 (1H, d), 7.60 (2H, d), 7.40 (3H, m), 3.20 (2H, m), 2.92 (2H, m), 2.80 (2H, m), 2.70 (3H, s), 2.30 (2H, m)	$[M+H]^+$ 439
68		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide	1. Method A1 using 2-amino-4-(4-chlorophenyl)-thiazole and Preparation K 2. Method L 3. Method B	^{1}H NMR (Me-d_3-OD) 7.98 (2H, s), 7.85 (2H, d), 7.60 (2H, d), 7.40 (2H, d), 7.39 (2H, d), 7.32 (1H, s), 3.05 (2H, m), 2.92 (2H, m), 2.68 (2H, m), 2.10 (2H, m)	$[M+H]^+$ 464

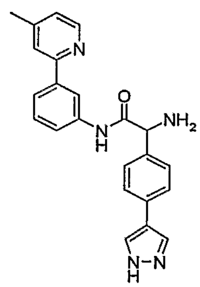
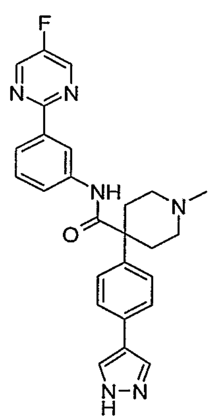
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
69		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(6-methyl-pyridazin-3-yl)-phenyl]-amide acetate	1. Method B using 3-Chloro-6-methyl-pyridazine and 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxa-borolan-2-yl)-phenylamine 2. Method A1 using Preparation K 3. Method L 4. Method B	^{1}H NMR (Me-d_3-OD) 8.21 (1H, s), 8.02 (1H, d), 7.98 (2H, s), 7.78 (1H, s), 7.69 (4H, m), 7.51 (3H, m), 3.43 (2H, m), 3.35 (2H, m), 2.85 (2H, m), 2.71 (3H, s), 2.35 (2H, m), 1.99 (3H, s)	$[M+H]^+$ 439
70		4-[4-(3-Methyl-1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide acetate	1. Method S 2. Method A1 using Preparation K 3. Method L 4. Method B using Preparation I 5. Method T	^{1}H NMR (Me-d_3-OD) 7.74 (1H, s), 7.53 (5H, m), 7.35 (1H, d), 7.23 (1H, t), 7.09 (1H, d), 3.42 (2H, m), 3.30 (2H, m), 2.80 (2H, m), 2.41 (3H, s), 2.30 (2H, m), 1.99 (3H, s), 1.30 (9H, s)	$[M+H]^+$ 441
71		4-[4-(3-Ethyl-1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide acetate	1. Method S 2. Method A1 using Preparation K 3. Method L 4. Method B using Preparation J 5. Method T	^{1}H NMR (Me-d_3-OD) 7.69 (1H, s), 7.55 (1H, s), 7.51 (4H, s), 7.33 (1H, d), 7.22 (1H, t), 7.10 (1H, d), 3.42 (2H, m), 3.33 (2H, m), 2.35 (4H, m), 2.30 (2H, m), 1.99 (3H, s), 1.32 (9H, s), 1.25 (3H, t)	$[M+H]^+$ 455

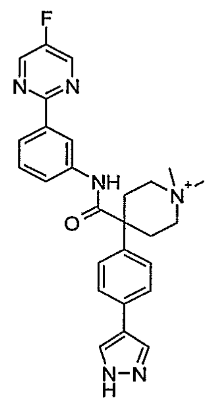
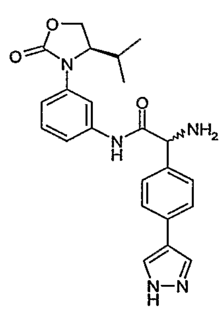
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
72		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-piperidin-1-yl-phenyl)-amide hydrochloride	1. Method A1 using Preparation A and 3-piperidin-4-yl-phenylamine hydrochloride 2. Method B2 3. Method V	1H NMR (Me-d3-OD) 8.59(2H, s), 8.23 (1H, 2), 7.79 (2H, d), 7.57 (5H, m), 3.64 (4H, m), 3.47 (2H, m), 3.32 (2H, m), 2.91 (2H, m), 2.41 (2H, m), 2.06 (4H, m), 1.84 (2H, m).	$[M+H]^+$ 430
73		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid methyl-(3-piperidin-1-yl-phenyl)-amide hydrochloride	1. Method N using (3-bromo-phenyl)-methylamine 2. Method F using piperidine 3. Method M using anisole as additive 4. Method A1 using Preparation K 5. Method L 6. Method B 7. Method V	1H NMR (Me-d3-OD) 8.04 (2H, s), 7.60 (2H, d), 7.29 (1H, m), 7.12 (3H, m), 6.70, (1H, m), 6.29 (1H, m), 3.37 (4H, m), 3.20 (3H, s), 2.97 (4H, m), 2.53 (2H, m), 2.02 (2H, m), 1.62 (4H, m), 1.45 (2H, m).	$[M-H^+]^-$ 442
74		2-{4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzooxazole hydrochloride	1. Method A1 using Preparation K and 2-aminophenol 2. Method W 3. Method L 4. Method B 5. Method V	1H NMR (Me-d3-OD) 8.21 (2H, s), 7.77 (1H, m), 7.68 (2H, d), 7.59 (1H, m)7.46 (2H, d), 7.42 (2H, m), 3.53 (2H, m), 3.28 (2H, m), 3.09 (2H, m), 2.59 (2H, m).	$[M+H]^+$ 345

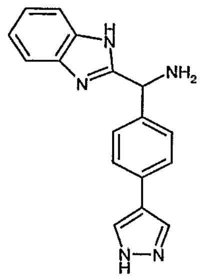
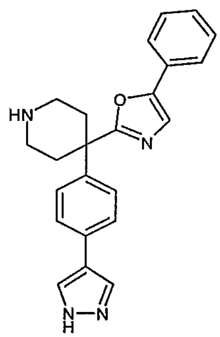
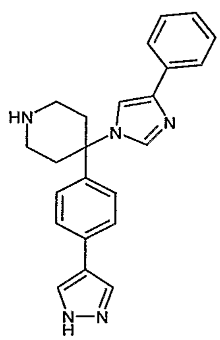
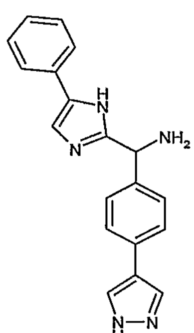
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
75		4'-Methoxy-biphenyl-3-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide, hydrochloride salt	1. Method A2 using Preparation H and 4'-methoxy-biphenyl-3-carboxylic acid 2. Method B 3. Method M	^{1}H NMR (DMSO-d_6) 9.12 (1H, m), 8.92 (1H, m), 8.66 (1H, s), 8.10 (1H, s), 8.07 (2H, s), 7.80 (2H, d), 7.71 (2H, d), 7.59 (2H, d), 7.54 (1H, t), 7.40 (2H, d), 7.07 (2H, d), 3.82 (3H, s), 3.25 (4H, m), 2.82 (2H, d), 2.25 (2H, m)	[M+H]$^+$ 453
76		6-(4-Methoxy-phenyl)-pyridine-2-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide, hydrochloride salt	1. Method A2 using Preparation H and 6-(4-methoxy-phenyl)-pyridine-2-carboxylic acid 2. Method B 3. Method M	^{1}H NMR (DMSO-d_6) 9.33 (1H, m), 9.09 (1H, m), 8.89 (1H, s), 8.31 (2H, d), 8.19 (1H, d), 8.14 (2H, s), 8.08 (1H, t), 7.87 (1H, d), 7.65 (2H, d), 7.50 (2H, d), 7.16 (2H, d), 3.91 (3H, s), 3.38 (2H, m), 3.20 (2H, m), 2.93 (2H, d), 2.42 (2H, m)	[M+H]$^+$ 454
77		3-(5-Methyl-tetrazol-1-yl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method A2 using Preparation H and 3-(5-methyl-tetrazol-1-yl)benzoic acid 2. Method B 3. Method M	^{1}H NMR (DMSO-d_6) 9.12 (1H, m), 8.95 (1H, m), 8.81 (1H, s), 8.20 (1H, s), 8.15 (1H, d), 8.06 (2H, s), 7.89 (1H, d), 7.78 (1H, t), 7.58 (2H, d), 7.39 (2H, d), 3.27 (4H, m), 2.81 (2H, d), 2.60 (3H, s), 2.24 (2H, m)	[M+H]$^+$ 429

Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
78		4-(4-Chloro-phenyl)-piperidine-4-carboxylic acid [3-(1H-pyrazol-4-yl)-phenyl]-amide	1. Method A1 using Preparation A and 3-iodoaniline 2. Method L 3. Method B1	^{1}H NMR (Me-d_3-OD) 7.94 (2H, s), 7.69 (1H, s), 7.49 (2H, d), 7.42 (2H, d), 7.33 (3H, m), 3.12 (2H, m), 3.04 (2H, m), 2.65 (2H, m), 2.08 (2H, m)	$[M+H]^+$ 381
79		2-Amino-2-(4-chloro-phenyl)-N-[3-(1H-pyrazol-4-yl)-phenyl]-acetamide	1. Method B2 using 3-iodoaniline 2. Method A2 using (4-bromo-phenyl)-tert-butoxy-carbonylamino-acetic acid 3. Method M	^{1}H NMR (Me-d_3-OD) 7.93 (2H, s), 7.82 (1H, s), 7.50 (2H, d), 7.39 (3H, d), 7.32 (2H, m), 4.65 (1H, s), 1.95 (3H, s).	$[M+H]^+$ 327
80		3-[(Z)-3,3-Dimethyl-1-(1H-pyrazol-4-yl)-but-1-enyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide	1. Method S using 3-iodoaniline and 3,3-dimethyl-1-butyne 2. Method A1 using Preparation A 3. Method L 4. Method B1	^{1}H NMR (Me-d_3-OD) 8.56 (1H, s), 7.98 (2H, br s), 7.66 (2H, d), 7.69 (2H, d), 7.43 (1H, d), 7.36 (1H, s), 7.25 (3H, br m), 6.99 (1H, d), 6.05 (1H, s), 3.25 (2H, m), 2.79 (2H, m), 2.28 (2H, m), 0.95 (9H, s).	$[M+H]^+$ 495

Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
81		N-(3-Benzooxazol-2-yl-phenyl)-2-piperazin-1-yl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate	1. Method A2 using 4-[(4-Bromo-phenyl)-carboxy-methyl]-piperazine-1-carboxylic acid tert-butyl ester and 3-Benzooxazol-2-yl-phenylamine 2. Method B2 3. Method M	^{1}H NMR (Me-d_3-OD) 8.55 (1H, s), 8.00 (3H, m), 7.80 (1H, d), 7.75 (1H, d), 7.67 (3H, m), 7.56 (3H, m), 7.43 (2H, m), 4.24 (1H, s), 3.30 (4H, m), 2.83 (4H, m), 1.97 (6H, s)	$[M+H]^+$ 477.17
82		2-Amino-N-[3-(5-methyl-thiazol-2-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate	1. Method B2 using 2-chloro-5-methyl-thiazole and 3-aminobenzene-boronic acid 2. Method A2 using (4-bromo-phenyl)-tert-butoxycarbonyl-amino-acetic acid 3. Method B2 4. Method M	^{1}H NMR (Me-d_3-OD) 8.19 (1H, s), 8.03 (2H, s), 7.72 (2H, d), 7.62 (4H, m), 7.54 (1H, s), 7.42 (1H, t), 5.09 (1H, s), 2.55 (3H, s), 1.99 (6H, s).	$[M+H]^+$ 390.10

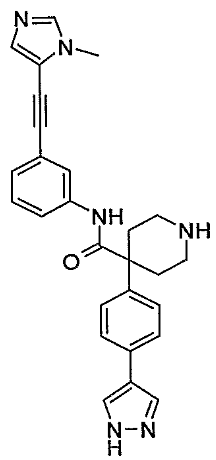
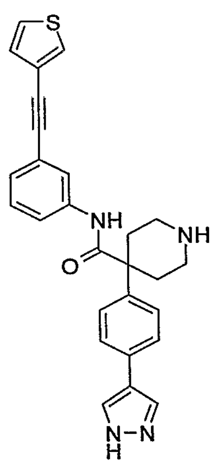
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
83		2-Amino-N-[3-(4-methyl-pyridin-2-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate	1. Method B2 using 2-bromo-4-methyl-pyridine and 3-aminobenzene-boronic acid 2. Method A2 using (4-bromo-phenyl)-tert-butoxycarbonyl-amino-acetic acid 3. Method B2 4. Method M	^{1}H NMR (Me-d_3-OD) 8.44 (1H, d), 8.17 (1H, m), 8.01 (2H, s), 7.68 (5H, m), 7.61 (2H, d), 7.45 (1H, t), 7.20 (1H, d), 5.08 (1H, s), 2.45 (3H, s), 1.98 (6H, s).	[M+H]$^+$ 384.15
84		1-Methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(5-fluoro-pyrimidin-2-yl)-phenyl]-amide	1. Method B2 using 2-chloro-5-fluoro-pyrimidine and 3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2. Method A1 using Preparation K 3. Method L 4. Method B2 5. Method X	^{1}H NMR (DMSO-d_6) 9.40 (1H, s), 8.98 (2H, s), 8.59 (1H, s), 8.02 (3H, br m), 7.81 (1H, d), 7.59 (2H, d), 7.43 (3H, m), 2.68 (4H, m), 2.18 (5H, m), 1.98 (2H, m).	[M+H]$^+$ 457.18

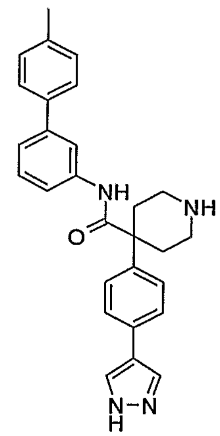
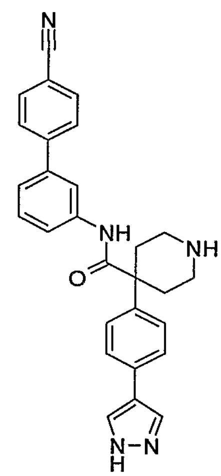
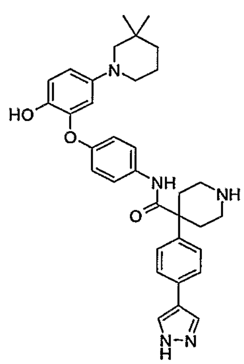
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
85		4-[3-(5-Fluoro-pyrimidin-2-yl)-phenylcarbamoyl]-1,1-dimethyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidinium	1. Method B2 using 2-chloro-5-fluoro-pyrimidine and 3-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2. Method A1 using Preparation K 3. Method L 4. Method B2 5. Method X	^{1}H NMR (Me-d_3-OD) 8.78 (2H, s), 8.52 (1H, s), 8.16 (1H, d), 8.00 (2H, s), 7.69 (3H, m), 7.57 (2H, d), 7.45 (1H, t), 3.63 (4H, m), 3.28 (3H, s), 3.23 (3H, s), 2.94 (2H, d), 2.60 (2H, m).	$[M+H]^+$ 471.19
86		2-Amino-N-[3-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide	1. Method F2 using (R)-4-isopropyl-2-oxazolidinone & 3-iodo-nitrobenzene 2. Method Q 3. Method A2 using racemic (4-bromo-phenyl)-tert-butoxy-carbonyl-amino-acetic acid 4. Method M 5. Method B2	^{1}H NMR (Me-d3-OD) 8.02 (2H, s), 7.88 (1H, d), 7.73 (2H, d), 7.58 (2H, d), 7.45 (1H, t), 7.38 (1H, t), 7.23 (1H, d), 4.59 (1H, m), 4.48 (1H, t), 4.33 (1H, m), 2.10 (1H, m), 0.93 (3H, d), 0.81 (3H, dd)	[M+H]+ 420

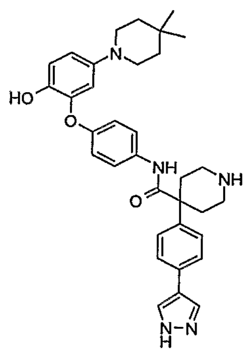
Example Number	Compound	Chemical Name	Method	N.M.R. Data	M.S.
87		C-(1H-Benzoimidazol-2-yl)-C-[4-(1H-pyrazol-4-yl)-phenyl]-methylamine	1. Preparation P 2. Method B1 3. Method M	^{1}H NMR (DMSO-d6) 12.90 (1H, br s), 12.21 (1H, br s), 8.20-7.80 (2H, br m), 7.59-7.39 (6H, m), 7.16-7.08 (2H, m), 5.27 (1H, s)	[M+H]+ 290.12
88		4-(5-Phenyl-oxazol-2-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine	1. Preparation L 2. Method L 3. Method B1	^{1}H NMR (Me-d3-OD) 7.95 (2H, s), 7.66 (2H, d), 7.59 (2H, d), 7.52 (1H, s), 7.43 (2H, t), 7.39-7.32 (3H, m), 3.27-3.19 (2H, m), 3.00-2.91 (2H, m), 2.88-2.80 (2H, m), 2.41-2.30 (2H, m)	[M+H]+ 371.17
89		4-(4-Phenyl-imidazol-1-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine	1. Preparation M 2. Method M 3. Method B1	^{1}H NMR (Me-d3-OD) 8.14 (1H, s), 7.98 (2H, s), 7.85 (1H, s), 7.79 (2H, d), 7.64 (2H, d), 7.39 (2H, t), 7.31-7.21 (3H, m), 3.51-3.43 (2H, m), 3.30-3.20 (2H, m), 3.05-2.86 (4H, m)	[M+H]+ 370.19
90		C-(5-Phenyl-1H-imidazol-2-yl)-C-[4-(1H-pyrazol-4-yl)-phenyl]-methylamine	1. Preparation N 2. Method 3. method M	^{1}H NMR (Me-d3-OD) 7.96 (2H, br s), 7.70 (2H, d), 7.59 (2H, d), 7.44-7.32 (5H, m), 7.27-7.21 (1H, m), 5.26 (1H, s)	[M+H]+ 316.12

EXAMPLES 91 TO 96

By following the methods described above, the compounds of Examples 91 to 96 set out in the Table below are prepared.

Ex. No.	Compound	Chemical Name	Synthetic Procedure
91		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3-methyl-3H-imidazol-4-ylethynyl)-phenyl]-amide	1. Procedure C using 5-ethynyl-1-methyl-1H-imidazole and 3-iodoaniline 2. Method A1 using Preparation A 3. Method L 4. Method B
92		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-thiophen-3-ylethynyl-phenyl)-amide	1. Procedure C using 3-ethynylthiophene and 3-iodoaniline 2. Method A1 using Preparation A 3. Method L 4. Method B

Ex. No.	Compound	Chemical Name	Synthetic Procedure
93		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methyl-biphenyl-3-yl)-amide	1. Method A1 using Preparation A and 4'-methyl-biphenyl-3-ylamine 2. Method L 3. Method B
94		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-cyano-biphenyl-3-yl)-amide	1. Method A1 using Preparation A and 3'-amino-biphenyl-4-carbonitrile 2. Method L 3. Method B
95		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[5-(3,3-dimethyl-piperidin-1-yl)-2-hydroxy-phenoxy]-phenyl}-amide	1. Method F using 3,3-dimethyl-piperidine and Preparation E 2. Method D1 3. Method E 4. Method A1 using Preparation A 5. Method L 6. Method N 7. Method B 8. Method P2

Ex. No.	Compound	Chemical Name	Synthetic Procedure
96		4-[4-(1H-Pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[5-(4,4-dimethyl-piperidin-1-yl)-2-hydroxy-phenoxy]-phenyl}-amide	1. Method F using Preparation E 2. Method D1 3. Method E 4. Method A1 using Preparation A 5. Method L 6. Method N 7. Method B 8. Method P2

BIOLOGICAL ACTIVITY

EXAMPLE 97

Measurement of PKA Kinase Inhibitory Activity (IC_{50})

Compounds of the invention can be tested for PK inhibitory activity using the PKA catalytic domain from Upstate Biotechnology (#14-440) and the 9 residue PKA specific peptide (GRTGRRNSI), also from Upstate Biotechnology (#12-257), as the substrate. A final concentration of 1 nM enzyme is used in a buffer that includes 20 mM MOPS pH 7.2, 40 µM ATP/γ^{33}P-ATP and 5 µM substrate. Compounds are added in dimethylsulphoxide (DMSO) solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. Unincorporated γ^{33}P-ATP is then separated from phosphorylated proteins on a Millipore MAPH filter plate. The plates are washed, scintillant is added and the plates are then subjected to counting on a Packard Topcount.

The % inhibition of the PKA activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

The compounds of Examples 1, 2, 3, 5, 9, 10, 11, 12, 13, 17, 19, 23, 25, 27, 28, 29, 30, 31, 32, 34, 35, 37, 38, 39, 41, 42, 44, 45, 46, 47, 48, 50, 51, 52, 54, 55, 58, 59, 62, 63, 64, 67, 68, 70, 72, 74, 75, 76, 77, 81, 82, 83, 84 and 87 all have IC_{50} values of less than 1µM

whereas the compounds of Examples 6, 20, 22, 33, 40, 43, 56, 57, 66, 78 and 86 have IC_{50} values of less than 5μM.

EXAMPLE 98

Measurement of PKB Kinase Inhibitory Activity (IC_{50})

The inhibition of protein kinase B (PKB) activity by compounds can be determined determined essentially as described by Andjelkovic *et al.* (Mol. Cell. Biol. 19, 5061-5072 (1999)) but using a fusion protein described as PKB-PIF and described in full by Yang et al (Nature Structural Biology 9, 940 – 944 (2002)). The protein is purified and activated with PDK1 as described by Yang *et al.* The peptide AKTide-2T (H-A-R-K-R-E-R-T-Y-S-F-G-H-H-A-OH) obtained from Calbiochem (#123900) is used as a substrate. A final concentration of 0.6 nM enzyme is used in a buffer that includes 20 mM MOPS pH 7.2, 30 μM ATP/γ^{33}P-ATP and 25 μM substrate. Compounds are added in DMSO solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. The reaction mixture is transferred to a phosphocellulose filter plate where the peptide binds and the unused ATP is washed away. After washing, scintillant is added and the incorporated activity measured by scintillation counting.

The % inhibition of the PKB activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

Following the protocol described above, the IC_{50} values of the compounds of Examples 1-4, 9-13, 17, 21, 23, 27, 28, 31, 36, 39, 41, 42, 46, 47, 51, 58, 60, 63, 68, 69, 70, 71, 74, 75, 81, 83 and 84 have been found to be less than 0.1 μM whilst the compounds of Examples 5, 6, 19, 20, 22, 24, 25, 33, 35, 37, 38, 40, 45, 48, 50, 52, 53, 54, 62, 64, 66, 67, 72, 78, 80, 82 and 87 each have IC_{50} values of less than 1 μM, the compounds of Examples 43, 44 and 77 each have IC_{50} values of less than 5 μM.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 99

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50 mg of the compound with 197mg of lactose (BP) as diluent, and 3 mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

(iii) Injectable Formulation I

A parenteral composition for administration by injection can be prepared by dissolving a compound of the formula (I) (e.g. in a salt form) in water containing 10% propylene glycol to give a concentration of active compound of 1.5 % by weight. The solution is then sterilised by filtration, filled into an ampoule and sealed.

(iv) Injectable Formulation II

A parenteral composition for injection is prepared by dissolving in water a compound of the formula (I) (e.g. in salt form) (2 mg/ml) and mannitol (50 mg/ml), sterile filtering the solution and filling into sealable 1 ml vials or ampoules.

(v) Injectable formulation III

A formulation for i.v. delivery by injection or infusion can be prepared by dissolving the compound of formula (I) (e.g. in a salt form) in water at 20 mg/ml. The vial is then sealed and sterilised by autoclaving.

(vi) Injectable formulation IV

A formulation for i.v. delivery by injection or infusion can be prepared by dissolving the compound of formula (I) (e.g. in a salt form) in water containing a buffer (e.g. 0.2 M acetate pH 4.6) at 20mg/ml. The vial is then sealed and sterilised by autoclaving.

(vii) Subcutaneous Injection Formulation

A composition for sub-cutaneous administration is prepared by mixing a compound of the formula (I) with pharmaceutical grade corn oil to give a concentration of 5 mg/ml. The composition is sterilised and filled into a suitable container.

(viii) Lyophilised formulation

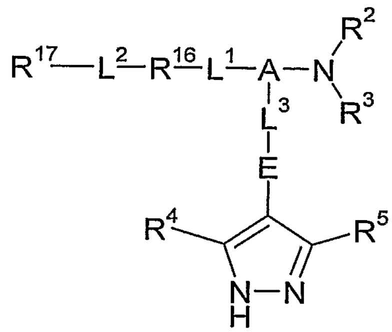
Aliquots of formulated compound of formula (I) are put into 50 ml vials and lyophilized. During lyophilisation, the compositions are frozen using a one-step freezing protocol at (–45 °C). The temperature is raised to –10 °C for annealing, then lowered to freezing at –45 °C, followed by primary drying at +25 °C for approximately 3400 minutes, followed by a secondary drying with increased steps if temperature to 50 °C. The pressure during primary and secondary drying is set at 80 millitor.

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the formula (I):



(I)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, C_1-C_4 alkyl, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl and C_{1-4} hydrocarbyloxycarbonyl wherein the hydrocarbyl, acyl and hydrocarbyloxycarbonyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, $-C(=NR^{11})-$, -C(S)-, $-NR^{11}-$, $C(=CHR^{11})$, -SO- and $-SO_2$-; R' is hydrogen or methyl;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms a monocyclic or bicyclic 5-12 membered heteroaryl ring system;

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously;

R^{16} is a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl,

C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN;

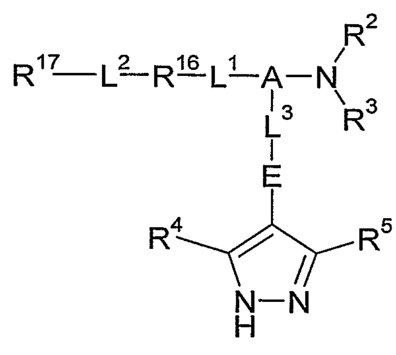
wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^{16} may themselves be further substituted by one or more substituents chosen from OH, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above;

L^2 is absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -O-, -S-, -C(O)-, C(=CHR^{11}), C(S)-, -NR^{11}-, $C_{3\text{-}4}$ cycloalkanediyl, -SO- and -SO_2-;

R^{17} is absent or is $C_{1\text{-}6}$ alkyl or a 5 to 12 membered saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN, R^q, OR^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent;

wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -N(R^{11})$_2$, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

2. A compound of the formula (I^0):



(I^0)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, C_1-C_4 alkyl, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO,

SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, -C(=NR^{11})-, -C(S)-, -NR^{11}-, C(=CHR^{11}), -SO- and -SO_2-; R' is hydrogen or methyl;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms an 8-12 membered fused bicyclic heteroaryl ring system;

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously;

R^{16} is a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN;

wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^{16} may themselves be further substituted by one or more substituents chosen from OH, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above;

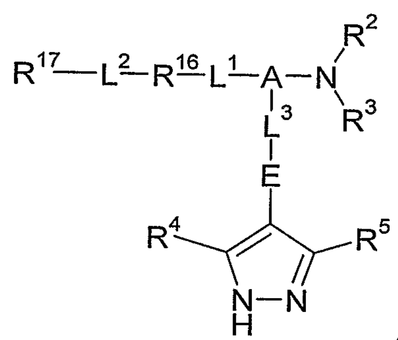
L^2 is absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -O-, -S-, -C(O)-, C(=CHR^{11}), C(S)-, -NR^{11}-, C_{3-4} cycloalkanediyl, -SO- and -SO_2-;

R^{17} is absent or is C_{1-6} alkyl or a 5 to 12 membered saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -

$C(O)OR^{11}$, COR^{11}, halogen, NO_2, CN, R^q, OR^q and $-Alk-R^q$ where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent;

wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, $-N(R^{11})_2$, $-O(C_1$-C_6 alkyl), -$CONHR^{11}$, $-NHCOR^{11}$, $-C(O)OR^{11}$, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

3. A compound according to claim 2 having the formula (Ia):



(Ia)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between L^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between L^3 and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, C_1-C_4 alkyl, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

L^1 is a bond or a linker selected from -CONH-, -NHCO-, -C(O)-, -C(S)-, -NR^{11}-, -SO- and -SO_2-;

each R^{11} is independently hydrogen or C_1-C_6 alkyl;

or L^1 together with the group R^{16} forms an 8-12 membered fused bicyclic heteroaryl ring system;

L^3 is a bond or a linker selected from CONH and HNCO; provided that L^1 and L^3 cannot both be linkers simultaneously; and provided also that L^1 and L^3 cannot both be a bond simultaneously;

R^{16} is a 5- to 12-membered saturated, unsaturated or partially saturated monocyclic or bicyclic carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN;

wherein the alkyl, alkenyl, alkynyl and alkoxy substituents of R^{16} may themselves be further substituted by one or more substituents chosen from OH, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2 or CN; and wherein R^{11} is as defined above;

L^2 is absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONH-, -NHCO-, -O-, -S-, -C(O)-, -C(S)-, -NR^{11}-, -SO- and -SO_2-;

R^{17} is absent or is C_{1-6} alkyl or a 5- or 6-membered saturated, unsaturated or partially saturated carbocyclic or heterocyclic ring which is optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN, R^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring; provided that when R^{17} is absent, then L^2 is also absent;

wherein the alkyl, alkenyl, alkynyl , cycloalkyl, carbocyclic heterocyclic and alkoxy substituents of R^{17} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -N(R^{11})$_2$, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above.

4. A compound according to any one of claims 1 to 3, wherein the linker group A has a maximum chain length of 3 atoms.

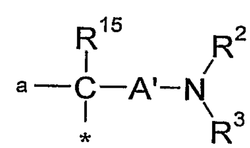
5. A compound according to any one of claims 1 to 4, wherein the linker group A has a chain length of 3 atoms extending between L^1 and NR^2R^3.

6. A compound according to any one of claims 1 to 5, wherein the linker group has a maximum chain length of 3 atoms extending between L^3 and NR^2R^3.

7. A compound according to any one of claims 1 to 6, wherein L^3 is a -C(O)NH- or a -NHC(O)- group.

8. A compound according to any one of claims 1 to 6, wherein L^3 is a bond.

9. A compound according to any one of claims 1 to 8, wherein the linker A has the formula:



wherein the letter "a" and the asterisk * denote the points of attachment to L^1 and L^3; A' is a linker as defined for A but which is up to 3 atoms in length; and R^{15} is hydrogen, OH or C_1-C_4 alkyl or, with the carbon atom to which it is attached, the linker A', R^2 and the nitrogen atom to which it is attached forms a 5 to 7 membered heterocyclic ring which optionally contains one or more additional heteroatoms.

10. A compound according to claim 9, wherein R^{15} is hydrogen, OH or methyl.

11. A compound according to claim 9 or claim 10 wherein the linker group A' is one or two atoms in length.

12. A compound according to any one of claims 9 to 11 wherein the linker group A' is an unsubstituted hydrocarbon chain.

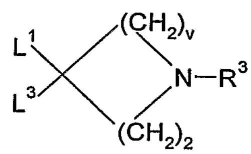
13. A compound according to claim 11 or claim 12, wherein the linker group A' is -CH_2- or -CH_2CH_2-.

14. A compound according to claim 9, wherein the linker group A', together with the CR^{15} moiety and the NR^3 moiety forms a 5 or 6 membered ring which may contain one or more additional heteroatoms.

15. A compound according to claim 14 where the ring is a 6-membered ring.

16. A compound according to claim 14 or claim 15, wherein the ring contains an oxygen atom.

17. A compound according to claim 14 or claim 15, wherein the linker group A is of the formula:



wherein L^1, L^3 and NR^2R^3 are not part of the linker A but are included to show how it is linked to the rest of the molecule;
v is 1 or 2; and
any one of the CH_2 groups may be replaced by a heteroatom, for example O.

18. A compound according to any one of claims 1 to 17 wherein L^1 is a bond or a linker selected from -CONH-, -NHCO-, -C(O)-, -C(S)-, $-NR^{11}-$, -SO- and $-SO_2-$; wherein R^{11} is hydrogen or C_1-C_6 alkyl; or L^1 together with the group R^{16} forms a 8-12 membered fused heteroaryl ring system.

19. A compound according to any one of claims 1 to 18 wherein L^1 is a bond or a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, $C(=CHR^{11})$, -C(S)-, -SO- and $-SO_2-$; wherein R' is hydrogen or methyl (preferably hydrogen), R^{11} is hydrogen or C_1-C_6 alkyl; or L^1 together with the group R^{16} forms a 8-12 membered fused heteroaryl ring system.

20. A compound according to any one of claims 1 to 17 wherein L^1 is a linker selected from C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -S-, -C(O)-, $C(=CHR^{11})$, -C(S)-, -SO- and $-SO_2-$; wherein R' is hydrogen or methyl (preferably hydrogen).

21. A compound according to any one of claims 1 to 17 wherein L^1 is C_1-C_4 alkenylene, C_1-C_4 alkynylene, –CONR'-, -NR'CO-, -C(O)- or C(=CHR^{11}) wherein R' is hydrogen or methyl (preferably hydrogen).

22. A compound according to any one of claims 1 to 17, wherein the linker L^1 is -CONH-, -NHCO- or -C(O)-.

23. A compound according to claim 22 wherein the linker L^1 is -CONH- or -NHCO-.

24. A compound according to any one of claims 1 to 17, wherein L^1 and R^{16} combine to form a 8-10 membered fused bicyclic heteroaryl ring system in which each ring is a 5 or 6 membered ring containing up to 3 nitrogen atoms and in which any of the ring CH groups can be replaced by a C=O.

25. A compound according to claim 24, wherein L^1 and R^{16} combine to form: (i) an indole, azaindole, purine or benzimidazole ring system; or (ii) an indole, azaindole, purine, benzoxazole, benzothiazole or benzimidazole ring system.

26. A compound according to any one of claims 1 to 25, wherein the group R^{16} is an aromatic group.

27. A compound according to claim 26, wherein R^{16} is a monocyclic aromatic group.

28. A compound according to claim 27, wherein R^{16} is phenyl.

29. A compound according to any one of claims 1 to 28, wherein R^{16} is unsubstituted or substituted by up to 5 substituents chosen from halogen, -O(C_1-C_4 alkyl), -O(C_1-C_4 haloalkyl) and hydroxy.

30. A compound according to any one of claims 1 to 29 wherein L^2 is absent or is a bond or a linker selected from C_1-C_4 alkylene, C_1-C_4 alkenylene, C_1-C_4 alkynylene, -CONH-, -NHCO-, -O-, -S-, -C(O)-, -C(S)-, -NR^{11}-, -SO- and -SO$_2$-.

31. A compound according to any one of claims 1 to 30, wherein L^2 is -C(O)-, -O-, -S-, -SO- or -SO$_2$-.

32. A compound according to claim 31 wherein L^2 is C(O)-, -O- or -SO$_2$-.

33. A compound according to any one of claims 1 to 30 wherein n is L^2 is a bond and R^{17} is directly linked to R^{16}.

34. A compound according to any one of claims 1 to 33 wherein R^{17} is a 5- or 6-membered aryl or heteroaryl group or a 5- or 6-membered cycloalkyl or heterocyclyl group.

35. A compound according to claim 34 wherein R^{17} is phenyl, pyridyl, morpholinyl, piperidinyl or piperazinyl.

36. A compound according to any one of claims 1 to 35 wherein R^{17} is phenyl, pyrimidinyl, pyridyl, pyridazinyl, morpholinyl, piperidinyl, piperazinyl; pyrazolyl, oxazolyl, triazolyl, tetrazolyl or benzoxazolyl.

37. A compound according to any one of claims 34 to 36 wherein R^{17} is unsubstituted or is substituted with halogen, hydroxy, $-N(R^{11})_2$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -$O(C_1$-C_4 alkyl), -$O(C_1$-C_4 haloalkyl), -$O(C_1$-C_4 alkyl)-$O(C_1$-C_4 alkyl), -O(C $_{5\text{-}6}$ carbocyclyl), -O($c_{5\text{-}6}$ heterocyclyl), a 5- or 6-membered carbocyclic or heterocyclic ring, -C_1-C_4 alkyl(carbocyclyl)or -C_1-C_4 alkyl(heterocyclyl).

38. A compound according to claim 37 wherein R^{17} is unsubstituted or is substituted with halogen, hydroxy, $-N(R^{11})_2$, -$O(C_1$-C_4 alkyl), -$O(C_1$-C_4 haloalkyl), -$O(C_1$-C_4 alkyl)-$O(C_1$-C_4 alkyl), -O(C $_{5\text{-}6}$ carbocyclyl), -O($c_{5\text{-}6}$ heterocyclyl), a 5- or 6-membered carbocyclic or heterocyclic ring, -C_1-C_4 alkyl(carbocyclyl)or -C_1-C_4 alkyl(heterocyclyl).

39. A compound according to any one of claims 34 to 38, wherein the R^{17} group has 0 to 3 substituents.

40. A compound according to any one of claims 1 to 30 wherein R^{17} and L^2 are both absent.

41. A compound according to any one of claims 1 to 40, wherein R^2 and R^3 are independently selected from hydrogen, methyl, cyclopropyl, cyclopropylmethyl and cyclobutyl.

42. A compound according to any one of claims 1 to 40, wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected

from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

43. A compound according to any one of the preceding claims, wherein R^4 is hydrogen, methyl or ethyl (preferably hydrogen or methyl, and more preferably hydrogen).

44. A compound according to any one of the preceding claims, wherein R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

45. A compound according to any one of claims 1 to 43, wherein R^5 is hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9b}$ and $NHCONHR^{9b}$ where R^{9b} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy or C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

46. A compound according to claim 45 wherein R^5 is hydrogen, methyl or ethyl (preferably hydrogen or methyl, and more preferably hydrogen).

47. A compound according to any one of the preceding claims wherein E is a monocyclic group.

48. A compound according to any one of the preceding claims wherein E is an aryl or heteroaryl group.

49. A compound according to claim 48 wherein E is selected from optionally substituted phenyl, thiophene, furan, pyrimidine and pyridine groups.

50. A compound according to claim 49 wherein E is a phenyl group.

51. A compound according to any one of claims 1 to 46 wherein E is a non-aromatic monocyclic group selected from cycloalkanes such as cyclohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone.

52. A compound according to any one of the preceding claims wherein the group A and the pyrazole group are attached to the group E in a *meta* or *para* relative orientation; i.e. A and the pyrazole group are not attached to adjacent ring members of the group E.

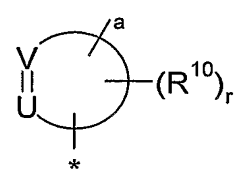
53. A compound according to claim 52 wherein E is selected from 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl.

54. A compound according to any one of the preceding claims wherein E is unsubstituted or has up to 4 substituents R^8 selected from hydroxy, oxo (when E is non-aromatic), chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

55. A compound according to claim 54 wherein E has 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent.

56. A compound according to claim 55 wherein E is unsubstituted.

57. A compound according to any one of the preceding claims wherein the group E is an aryl or heteroaryl group having five or six members and containing up to three heteroatoms selected from O, N and S, the group E being represented by the formula:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;
r is 0, 1 or 2;
U is selected from N and CR^{12a}; and
V is selected from N and CR^{12b}; where R^{12a} and R^{12b} are the same or different and each is hydrogen or a substituent containing up to ten atoms selected from C, N, O, F, Cl and S provided that the total number of non-hydrogen atoms present in R^{12a} and R^{12b} together does not exceed ten;

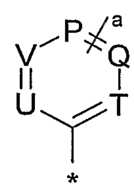
or R^{12a} and R^{12b} together with the carbon atoms to which they are attached form an unsubstituted five or six membered saturated or unsaturated ring containing up to two heteroatoms selected from O and N; and

R^{10} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

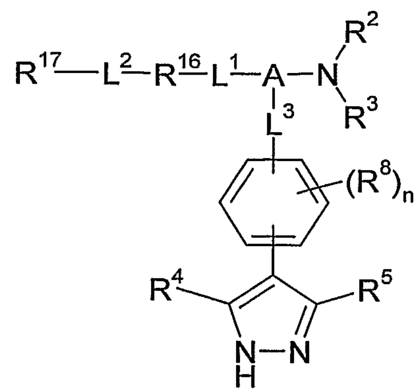
58. A compound according to claim 57 wherein E is represented by the formula:



where P, Q and T are the same or different and are selected from N, CH and NCR^{10}, provided that the group A is attached to a carbon atom.

59. A compound according to claim 58 wherein the group E is selected from groups B1 to B13 in Table 2.

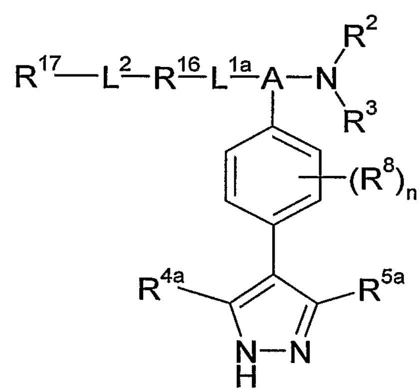
60. A compound according to any one of claims 1 to 3 having the formula (II):



(II)

wherein n is 0, 1, 2 or 3 and R^2, R^3, R^4, R^5, R^8, R^{16}, R^{17}, L^1, L^2, L^3 and A are as defined in any one of the preceding claims.

61. A compound according to claim 60 having the formula (III):

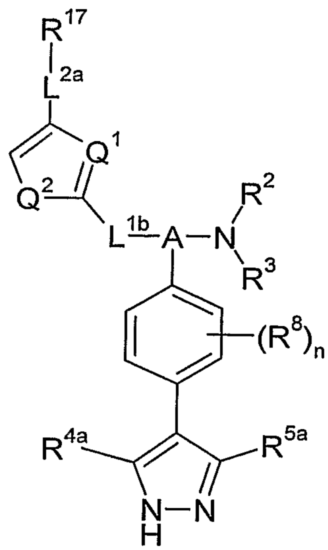


(III)

wherein R^{4a} is selected from hydrogen, halogen, methyl, methoxy, cyano, and CF_3; R^{5a} is selected from hydrogen, halogen, methyl, methoxy, cyano, CF_3 and $CONH_2$; and L^{1a} is selected from C(O)NH and NHC(O) or, together with the group R^{16} forms an 8-12 membered fused bicyclic heteroaryl ring system selected from benzoimidazole and benzoxazole; n is 0, 1 or 2 and A, R^2, R^3, R^8 and R^{17} are as defined in any one of the preceding claims.

62. A compound according to claim 61 wherein R^{16} is a five or six membered aryl or heteroaryl group, such as a phenyl group, pyridyl group or a five membered heteroaryl ring containing up to two heteroatoms selected from O, N and S (for example imidazole, thiazole or thiophene).

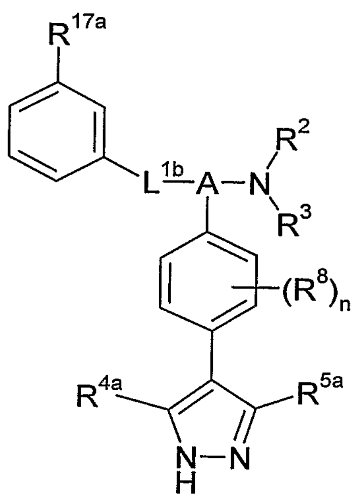
63. A compound according to claim 61 or claim 62 which is represented by formula (IV):



(IV)

wherein L^{1b} is NHC(O) or C(O)NH; L^{2a} is bond or an ethynylene group; Q^1 is CH or N; Q^2 is CH=CH or S; and n, A, R^2, R^3, R^{4a}, R^{5a}, R^8 and R^{17} are as defined in any one of the preceding claims.

64. A compound according to claim 63 having the formula (V):



(V)

wherein R^{17a} is selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, piperidinyl, piperazinyl, pyrazolyl, oxazolyl, triazolyl, tetrazolyl, thiazolyl, oxo-oxazolidinyl, and benzoxazolyl, each optionally substituted by one or more substituents selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, -O(C_1-C_6 alkyl), -OH, -N(R^{11})$_2$, -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN, R^q, OR^q and -Alk-R^q where Alk is a straight chain or branched alkylene group of 1 to 4 carbon atoms

and R^q is a 5 to 7 membered saturated or unsaturated carbocyclic or heterocyclic ring;
wherein the alkyl, alkenyl, alkynyl , cycloalkyl, heterocyclyl, and alkoxy substituents of R^{17a} may themselves be further substituted by one or more substituents chosen from C_1-C_6 alkyl, OH, -N(R^{11})$_2$, -O(C_1-C_6 alkyl), -CONHR^{11}, -NHCOR^{11}, -C(O)OR^{11}, COR^{11}, halogen, NO_2, CN or a carbocyclic or heterocyclic ring; and wherein R^{11} is as defined above, and n, A, R^2, R^3, R^{4a}, R^{5a} and R^8 are as defined in any one of the preceding claims.

65. A compound according to claim 64 wherein R^{17a} is selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, piperidinyl, piperazinyl, pyrazolyl, oxazolyl, triazolyl, tetrazolyl, benzoxazolyl, each being optionally substituted as defined in claim 64.

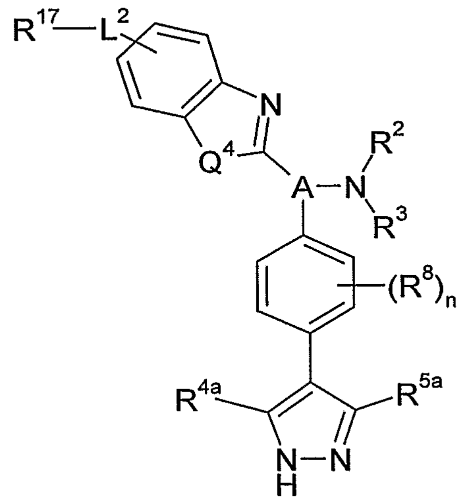
66. A compound according to claim 64 or 65 wherein the substituents for R^{17a} are selected from halogen, trifluoromethyl, C_1-C_6 alkyl, and -O(C_1-C_6 alkyl).

67. A compound according to any one of claims 64 to 66 wherein there are 0-2 substituents present on R^{17a}.

68. A compound according to claim 67 wherein R^{17a} is an unsubstituted group.

69. A compound according to claim 67 wherein R^{17a} is unsubstituted or is substituted by a single substituent selected from chlorine, fluorine, methyl, methoxy and trifluoromethyl.

70. A compound according to claim 61 which is represented by the formula (VI):



(VI)

wherein Q^4 is NH, S or O and n, L^2, R^2, R^3, R^{4a}, R^{5a}, R^8 and R^{17} are as defined in any one of the preceding claims.

71. A compound according to claim 70 wherein Q^4 is NH or O.

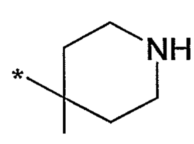
72. A compound according to claim 70 or claim 71 wherein L^2 is O, or L^2 is a bond and R^{17} is a bond.

73. A compound according to any one of claims 61 to 72 wherein R^{4a} is selected from hydrogen and methyl, and more preferably is hydrogen.

74. A compound according to any one of claims 61 to 73 wherein R^{5a} is selected from hydrogen and methyl, and more preferably is hydrogen.

75. A compound according to any one of claims 61 to 74 wherein both R^{4a} and R^{5a} are hydrogen.

76. A compound according to any one of the preceding claims wherein the moiety A-NR^2R^3 forms the group:



where the asterisks indicate the points of attachment to neighbouring groups.

77. A compound according to any one of claims 60 to 76 wherein, for the moiety $(R^8)_n$, n is 0, 1 or 2, but more preferably is 0 or 1 and most preferably is 0.

78. A compound according to any one of the preceding claims having a molecular weight no greater than 1000, more usually less than 750, for example less than 700, or less than 650, or less than 600, or less than 550.

79. A compound according to claim 78 wherein the molecular weight is less than 525 and, for example, is 500 or less.

80. A compound of formula (I) which is:
N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-3-methoxy-benzamide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-methoxy-phenyl)-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-chloro-phenyl)-amide;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3,4-dichloro-phenyl)-amide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-piperidin-1-yl-phenoxy)-phenyl]-amide diacetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-methoxy-phenoxy)-phenyl]-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(2-hydroxy-phenoxy)-phenyl]-amide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(piperidin-4-yloxy)-phenyl]-amide tritrifluoroacetate;
2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diacetate
6-(3-methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diformate;
dimethyl-[3-(2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-3H-benzoimidazol-5-yloxy)-phenyl]-amine diformate;
6-(2-methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole acetate;

6-(4-methoxy-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(2-hydroxy-5-piperidin-1-yl-phenoxy)-phenyl]-amide acetate;

4-(3-piperidin-1-yl-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-morpholin-4-yl-phenyl)-amide diformate;

N-{2-methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-benzamide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4-phenoxy-phenyl)-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-dimethylamino-phenoxy)-phenyl]-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-trifluoromethoxy-phenoxy)-phenyl]-amide acetate;

6-phenoxy-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[3-(3,3-dimethyl-piperidin-1-yl)-phenoxy]-phenyl}-amide;

6-(3-piperidin-1-yl-phenoxy)-2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-1H-benzoimidazole triacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-isopropoxy-phenoxy)-phenyl]-amide acetate;

4-(4-morpholin-4-ylmethyl-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-{4-[4-(4-methyl-piperazin-1-ylmethyl)-benzoyl]-benzoylamino}-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester;

4-[4-(4-methyl-piperazin-1ylmethyl)-benzoyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(3-methoxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(2-methoxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(2-hydroxy-phenoxy)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-benzamide;

4-(3-morpholin-4-ylmethyl-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-[3-(4-methyl-piperazin-1-ylmethyl)-benzoyl]-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-4-chloro-benzamide;

N-{3-amino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-3-chloro-benzamide;

N-{3-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-4-phenoxy-benzamide;

N-{3-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-4-benzene sulphonyl-benzamide;

N-[3-amino-1-(4-chloro-phenyl)-propyl]-3-(1H-pyrazol-4-yl)-benzamide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-cyclopentyloxy-phenoxy)-phenyl]-amide formate;

N-[{-amino-1-(4-(1H-pyrazol-4-yl)-phenyl]-propy}-benzoyl-benzamide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3-methyl-3H-imidazol-4-ylethynyl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-thiophen-3-ylethynyl-phenyl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4-methyl-piperazin-1-yl)-phenyl]-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4,4-dimethyl-piperidin-1-yl)-phenyl]-amide;

4-[4-(1H-pPyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methyl-biphenyl-3-yl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methoxy-biphenyl-3-yl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-cyano-biphenyl-3-yl)-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[5-(3,3-dimethyl-piperidin-1-yl)-2-hydroxy-phenoxy]-phenyl}-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid {4-[5-(4,4-dimethyl-piperidin-1-yl)-2-hydroxy-phenoxy]-phenyl}-amide;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (4'-methoxy-biphenyl-3-yl)-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3'-methyl-biphenyl-4-yl)-amide;

cyclohexanecarboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate;

4'-trifluoromethyl-biphenyl-3-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(1H-pyrazol-4-yl)-phenyl]-amide;

2-amino-N-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide acetate;

2-amino-N-(4'-methoxy-biphenyl-3-yl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide acetate;

1-benzoyl-piperidine-4-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-pyrimidin-2-yl-phenyl)-amide diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-amide diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-pyridin-3-yl-phenyl)-amide diacetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-tert-butyl-phenyl)-amide acetate;

4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-benzooxazol-2-yl-phenyl)-amide diacetate;

2-amino-N-(3-tert-butyl-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride;

2-amino-N-(3-isopropoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(5-fluoro-pyrimidin-2-yl)-phenyl]-amide diacetate;
2-amino-N-(3-benzooxazol-2-yl-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide hydrochloride;
2-amino-N-[3-(3,3-dimethyl-but-1-ynyl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;
2-amino-N-[3-(3,3-dimethyl-but-1-ynyl)-phenyl]-2-[4-(5-ethyl-1H-pyrazol-4-yl)-phenyl]-acetamide;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-oxazol-5-yl-phenyl)-amide diacetate;
4-(5-phenyl-1H-imidazol-2-yl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(3-cyclopentyloxy-phenoxy)-phenyl]-amide formate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(2-methyl-pyrimidin-4-yl)-phenyl]-amide trihydrochloride;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [4-(4-chloro-phenyl)-thiazol-2-yl]-amide;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(6-methyl-pyridazin-3-yl)-phenyl]-amide acetate;
4-[4-(3-methyl-1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide acetate;
4-[4-(3-ethyl-1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(3,3-dimethyl-but-1-ynyl)-phenyl]-amide acetate;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid (3-piperidin-1-yl-phenyl)-amide hydrochloride;
4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid methyl-(3-piperidin-1-yl-phenyl)-amide hydrochloride;
2-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzooxazole hydrochloride;
4'-methoxy-biphenyl-3-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide, hydrochloride salt;
6-(4-methoxy-phenyl)-pyridine-2-carboxylic acid {4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-amide, hydrochloride salt;

3-(5-methyl-tetrazol-1-yl)-N-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzamide;
N-(3-benzooxazol-2-yl-phenyl)-2-piperazin-1-yl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate;
2-amino-N-[3-(5-methyl-thiazol-2-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate;
2-amino-N-[3-(4-methyl-pyridin-2-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide diacetate;
1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine-4-carboxylic acid [3-(5-fluoro-pyrimidin-2-yl)-phenyl]-amide;
4-[3-(5-fluoro-pyrimidin-2-yl)-phenylcarbamoyl]-1,1-dimethyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidinium;
2-amino-N-[3-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;
C-(1H-benzoimidazol-2-yl)-C-[4-(1H-pyrazol-4-yl)-phenyl]-methylamine;
or a salt, solvate, tautomer or N-oxide thereof.

81. A compound according to any one of the preceding claims in the form of a salt, solvate (such as a hydrate), ester or N-oxide.

82. A compound as defined in any one of claims 1 to 81 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

83. The use of a compound as defined in any one of claims 1 to 81 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

84. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 81.

85. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound as defined in any one of claims 1 to 81 in an amount effective in inhibiting abnormal cell growth.

86. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 81 in an amount effective to inhibit PKB activity.

87. A method of inhibiting a protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 81.

88. A method of modulating a cellular process by inhibiting the activity of a protein kinase B using a compound as defined in any one of claims 1 to 81.

89. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 81 in an amount effective to inhibit PKB activity.

90. A compound as defined in any one of claims 1 to 81 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

91. The use of a compound as defined in any one of claims 1 to 81 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

92. The use of a compound of the formula (I) as defined in any one of claims 1 to 81 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth.

93. The use of a compound of the formula (I) as defined in any one of claims 1 to 81 for the manufacture of a medicament for the prophylaxis or treatment of a disease in which there is a disorder of proliferation, apoptosis or differentiation.

94. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 81.

95. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 81 in an amount effective to inhibit PKA.

96. A method of inhibiting a protein kinase A, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 81.

97. A method of modulating a cellular process by inhibiting the activity of a protein kinase A using a compound as defined in any one of claims 1 to 81.

98. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 81 in an amount effective to inhibit PKA activity.

99. A method of inducing apoptosis in a cancer cell, which method comprises contacting the cancer cell with a compound as defined in any one of claims 1 to 81.

100. A compound as defined in any one of claims 1 to 81 for the prophylaxis or treatment of any one of the disease states or conditions disclosed herein.

101. A compound as defined in any one of claims 1 to 81 for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase A.

102. A compound as defined in any one of claims 1 to 81 for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase B.

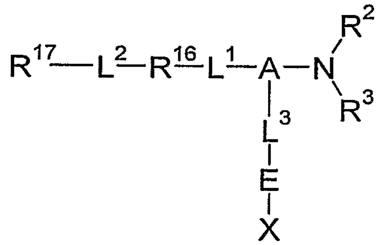
103. A pharmaceutical composition comprising a novel compound as defined in any one of claims 1 to 81 and a pharmaceutically acceptable carrier.

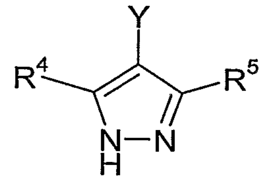
104. A compound as defined in any one of claims 1 to 81 for use in medicine.

105. A compound as defined in any one of claims 1 to 81 for use in medicine.

106. A process for the preparation of a compound of the formula (I) as defined in any one of claims 1 to 81, which process comprises:

the reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:


(X)


(XI)

wherein A, E, L^1, L^2, L^3, R^2 to R^5, R^{16} and R^{17} are as defined in any one of the preceding claims, one of the groups X and Y is selected from chlorine, bromine, iodine and trifluoromethanesulphonate, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue, in the presence of a palladium catalyst and a base.